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AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

VOLUME 84
2007

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Division of the American Chemical Society, Polskie Towarzystwo Chemiczne, Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. The hard cover edition is published by John Wiley and Sons, Inc., in the traditional format, and it differs in content primarily by the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Incorporation of graphical abstracts into the Table of Contents began with Volume 77. Annual volumes 70–74 and 75–79 have been incorporated into five-year versions of the collective volumes of *Organic Syntheses* that appeared as Collective Volume IX and X in the traditional hard cover format, available for purchase from the publishers. The Editors hope that the new Collective Volume series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

Organic Syntheses, Inc., joined the age of electronic publication in 2001 with the release of its free web site (www.orgsyn.org) followed in 2003 with the completion of a commercially available electronic database (www.mrw.interscience.wiley.com/osdb). Organic Syntheses, Inc., fully funded the creation of the free website at www.orgsyn.org in a partnership with CambridgeSoft Corporation and Data-Trace Publishing Company. The site is accessible to most internet browsers using Macintosh and Windows operating systems and may be used with or without a ChemDraw plugin. Because of continually evolving system requirements, users should review software compatibility at the website prior to use. John Wiley & Sons, Inc., and Accelrys, Inc., partnered with Organic Syntheses, Inc., to develop the new database (www.mrw.interscience.wiley.com/osdb) that is available for license with internet solutions from John Wiley & Sons, Inc. and intranet solutions from Accelrys, Inc.

Both the commercial database and the free website contain all annual and collective volumes and indices of *Organic Syntheses*. Chemists can draw structural queries and combine structural or reaction transformation queries with full-text and bibliographic search terms, such as chemical name, reagents, molecular formula, apparatus, or even hazard warnings or phrases. The preparations are categorized into reaction types, allowing search by category. The contents of individual or collective volumes can be browsed by lists of titles, submitters' names, and volume and page references, with or without reaction equations.

The commercial database at www.mrw.interscience.wiley.com/osdb also enables the user to choose his/her preferred chemical drawing package, or to utilize several freely available plug-ins for entering queries. The user is also able to cut and paste existing structures and reactions directly into the structure search query or their preferred chemistry editor, streamlining workflow. Additionally, this database contains links to the full text of primary literature references via CrossRef, ChemPort, Medline, and ISI Web of Science. Links to local holdings for institutions using open url technology can also be enabled. The database user can limit his/her search to, or order the search results by, such factors as reaction type, percentage yield, temperature, and publication date, and can create a customized table of reactions for comparison. Connections to other Wiley references are currently made via text search, with cross-product structure and reaction searching to be added in the coming year. Incorporations of new preparations will occur as new material becomes available.

INFORMATION FOR AUTHORS OF PROCEDURES

Organic Syntheses welcomes and encourages submissions of experimental procedures that lead to compounds of wide interest or that illustrate important new developments in methodology. Proposals for *Organic Syntheses* procedures will be considered by the Editorial Board upon receipt of an outline proposal as described below. A full procedure will then be invited for those proposals determined to be of sufficient interest. These full procedures will be evaluated by the Editorial Board, and if approved, assigned to a member of the Board for checking. In order for a procedure to be accepted for publication, each reaction must be successfully repeated in the laboratory of a member of the Editorial Board at least twice, with similar yields (generally ±5%) and selectivity to that reported by the submitters.

Organic Syntheses Proposals

A cover sheet should be included providing full contact information for the principal author and including a scheme outlining the proposed reactions (an Organic Syntheses Proposal Cover Sheet can be downloaded at orgsyn.org). Attach an outline proposal describing the utility of the methodology and/or the usefulness of the product. Identify and reference the best current alternatives. For each step, indicate the proposed scale, yield, method of isolation and purification, and how the purity of the product is determined. Describe any unusual apparatus or techniques required, and any special hazards associated with the procedure. Identify the source of starting materials. Enclose copies of relevant publications (attach pdf files if an electronic submission is used).

Submit proposals by mail or as e-mail attachments to:

Professor Charles K. Zercher
Associate Editor, *Organic Syntheses*
Department of Chemistry
University of New Hampshire
23 College Road, Parsons Hall
Durham, NH 03824

For electronic submissions: *org.syn@unh.edu*

Submission of Procedures

Authors invited by the Editorial Board to submit full procedures should prepare their manuscripts in accord with the Instructions to Authors, which are described below or may be downloaded at orgsyn.org. Submitters are also encouraged to consult earlier volumes of *Organic Syntheses* for models with regard to style, format, and the level of experimental detail expected in *Organic Syntheses* procedures. Manuscripts should be submitted to the Associate Editor. Electronic submissions are encouraged; procedures will be accepted as e-mail attachments in the form of Microsoft Word files with all schemes and graphics also sent separately as ChemDraw files.

Procedures that do not conform to the Instructions to Authors with regard to experimental style and detail will be returned to authors for correction. Authors will be notified when their manuscript is approved for checking by the Editorial Board, and it is the goal of the Board to complete the checking of procedures within a period of no more than six months.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Associate Editor. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Volume Editor felt was more appropriate. The Chemical Abstracts indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic Chemical Abstracts nomenclature, used in the Collective Indexes for the title compound, and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Chemical Abstracts Registry numbers, which are useful in computer searching and identification, are also provided in these appendices. Whenever two names are concurrently in use and one name is the correct Chemical Abstracts name, that name is preferred.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Merck & Co. and Pfizer, Inc. to the success of this enterprise through their support, in the form of time and expenses, of members of the Board of Editors.

INSTRUCTIONS TO AUTHORS

All organic chemists have experienced frustration at one time or another when attempting to repeat reactions based on experimental procedures found in journal articles. To ensure reproducibility, *Organic Syntheses* requires experimental procedures written with considerably more detail as compared to the typical procedures found in other journals and in the "Supporting Information" sections of papers. In addition, each *Organic Syntheses* procedure is carefully "checked" for reproducibility in the laboratory of a member of the Board of Editors.

Even with these more detailed procedures, the experience of *Organic Syntheses* editors is that difficulties often arise in obtaining the results and yields reported by the submitters of procedures. To expedite the checking process and ensure success, we have prepared the following "Instructions for Authors" as well as a *Checklist for Authors* and *Characterization Checklist* to assist you in confirming that your procedure conforms to these requirements. These checklists, which are available at orgsyn.org, should be completed and submitted together with your procedure. Procedures submitted to *Organic Syntheses* will be carefully reviewed upon receipt and procedures lacking any of the required information will be returned to the submitters for revision.

Scale and Optimization

The appropriate scale for procedures will vary widely depending on the nature of the chemistry and the compounds synthesized in the procedure. However, some general guidelines are possible. For procedures in which the principal goal is to illustrate a synthetic method or strategy, it is expected, in general, that the procedure should result in at least 5 g and no more than 50 g of the final product. In cases where the point of the procedure is to provide an efficient method for the preparation of a useful reagent or synthetic building block, the appropriate scale may be larger, but in general should not exceed 100 g of final product. Exceptions to these guidelines may be granted in special circumstances. For example, procedures describing the preparation of reagents employed as catalysts will often be acceptable on a scale of less than 5 g.

In considering the scale for an *Organic Syntheses* procedure, authors should also take into account the cost of reagents and starting materials. In general, the Editors will not accept procedures for checking in which the cost of any one of the reactants exceeds $500 for a single full-scale run. Authors are requested to identify the most expensive reagent or starting material on the procedure submission checklist and to estimate its cost per run of the procedure.

It is expected that all aspects of the procedure will have been optimized by the authors prior to submission, and that each reaction will have been carried out at least twice on exactly the scale described in the procedure. It is appropriate to report the weight, yield, and purity of the product of each step in the procedure as a range. In any case where a reagent is employed in significant excess, a Note should be included explaining why an excess of that reagent is necessary. If possible, the Note should indicate the effect of using amounts of reagent less than that specified in the procedure.

Reaction Apparatus

Describe the size and type of flask (number of necks) and indicate how *every* neck is equipped.

> "A 500-mL, three-necked, round-bottomed flask equipped with an overhead mechanical stirrer, 250-mL pressure-equalizing addition funnel fitted with an argon inlet, and a rubber septum is charged with. . . ."

Indicate how the reaction apparatus is dried and whether the reaction is conducted under an inert atmosphere. This can be incorporated in the text of the procedure or included in a Note.

> "The apparatus is flame-dried and maintained under an atmosphere of argon during the course of the reaction."

In the case of procedures involving unusual glassware or especially complicated reaction setups, authors are encouraged to include a photograph or drawing of the apparatus in the text or in a Note (for examples, see *Org. Syn.,* Vol. 82, 99 and Coll. Vol. X, pp 2, 3, 136, 201, 208, and 669).

Reagents and Starting Materials

All chemicals employed in the procedure must be commercially available or described in an earlier *Organic Syntheses* or *Inorganic Syntheses* procedure. For other compounds, a procedure should be included either as one or more steps in the text or, in the case of relatively straightforward preparations of reagents, as a Note. In the latter case, all requirements with regard to characterization, style, and detail also apply.

In one or more Notes, indicate the purity or grade of each reagent, solvent, etc. It is desirable to also indicate the source (company the chemical was purchased from), particularly in the case of chemicals where it is suspected that the composition (trace impurities, etc.) may vary from one supplier to another. In cases where reagents are purified, dried, "activated" (e.g., Zn dust), etc., a detailed description of the procedure used should be included in a Note. In other cases, indicate that the chemical was "used as received".

> "Diisopropylamine (99.5%) was obtained from Aldrich Chemical Co., Inc. and distilled under argon from calcium hydride before use. THF (99+%) was obtained from Mallinckrodt, Inc. and distilled from sodium benzophenone ketyl. Diethyl ether (99.9%) was purchased from Aldrich Chemical Co., Inc. and purified by pressure filtration under argon through activated alumina. Methyl iodide (99%) was obtained from Aldrich Chemical Co., Inc. and used as received."

The amount of each reactant should be provided in parentheses in the order mL, g, mmol, and equivalents with careful consideration to the correct number of significant figures.

Reaction Procedure

Describe every aspect of the procedure clearly and explicitly. Indicate the order of addition and time for addition of all reagents and how each is added (via syringe, addition funnel, etc.).

Indicate the temperature of the reaction mixture (preferably internal temperature). Describe the type of cooling (e.g., "dry ice-acetone bath") and heating (e.g., oil bath, heating mantle) methods employed. Be careful to describe clearly all cooling and warming cycles, including initial and final temperatures and the time interval involved.

Describe the appearance of the reaction mixture (color, homogeneous or not, etc.) and describe all significant changes in appearance during the course of the reaction (color changes, gas evolution, appearance of solids, exotherms, etc.).

In the case of reactions monitored by TLC, provide details in a Note, including eluent, R_f values, and method of visualization. For reactions followed by GC, HPLC, or NMR analysis, provide details on analysis conditions and relevant diagnostic peaks.

> "The progress of the reaction was followed by TLC analysis on silica gel with 20% EtOAc-hexane as eluent and visualization with *p*-anisaldehyde. The ketone starting material has $R_f = 0.40$ (green) and the alcohol product has $R_f = 0.25$ (blue)."

Reaction Workup

Details should be provided for reactions in which a "quenching" process is involved. Describe the composition (concentration should be described by molarity) and volume of quenching agent, and time and temperature for addition. In cases where reaction mixtures are added to a quenching solution, be sure to also describe the setup employed.

> "The resulting mixture is stirred at room temperature for 15 h, and then carefully poured over 10 min into a rapidly stirred, ice-cold aqueous solution of 1N HCl in a 500-mL Erlenmeyer flask equipped with a magnetic stirbar."

For extractions, the number of washes and the volume of each should be indicated.

For concentration of solutions after workup, indicate the method and pressure and temperature used.

> "The reaction mixture is diluted with 200 mL of water and transferred to a 500-mL separatory funnel, and the aqueous phase is separated and extracted with three 100-mL portions of ether. The combined organic layers are washed with 75 mL of water and 75 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (25 °C, 20 mmHg) to afford 3.25 g of a yellow oil."

> "The solution is transferred to a 250-mL, round-bottomed flask equipped with a magnetic stirbar and a 15-cm Vigreux column fitted with a short path distillation head, and then concentrated by careful distillation at 50 mmHg (bath temperature gradually increased from 25 to 75 °C)."

In cases where solid products are filtered, describe the type of filter funnel used and the amount and composition of solvents used for washes.

> “. . . and the resulting pale yellow solid is collected by filtration on a Büchner funnel and washed with 100 mL of cold (0 °C) hexanes.”

When solid or liquid compounds are dried under vacuum, indicate the pressure employed (rather than stating “reduced pressure” or “dried *in vacuo*”).

> ”. . . and concentrated at room temperature by rotary evaporation (20 mmHg) and then at 0.01 mmHg to provide. . . .”

> “The resulting colorless crystals are transferred to a 50-mL, round-bottomed flask and dried overnight in a 100°C oil bath at 0.01 mmHg.”

Purification: Distillation

Describe distillation apparatus including the size and type of distillation column. Indicate temperature (and pressure) at which all significant fractions are collected.

> “. . .and transferred to a 100-mL, round-bottomed flask equipped with a magnetic stirbar. The product is distilled under vacuum through a 12-cm, vacuum-jacketed column of glass helices (Note 16) topped with a Perkin triangle. A forerun (ca. 2 mL) is collected and discarded, and the desired product is then obtained, distilling at 50–55°C (0.04–0.07 mmHg). . . .”

Purification: Column Chromatography

Provide information on TLC analysis in a Note, including eluent, R_f values, and method of visualization.

Provide dimensions of column and amount of silica gel used; in a Note indicate source and type of silica gel.

Provide details on eluents used, and number and size of fractions.

> “The product is charged on a column (5 × 10 cm) of 200 g of silica gel (Note 15) and eluted with 250 mL of hexanes. At that point, fraction collection (25-mL fractions) is begun, and elution is continued with 300 mL of 2% EtOAc-hexanes and then 500 mL of 5% EtOAc-hexanes. The desired product is obtained in fractions 24–30, which are concentrated by rotary evaporation (25°C, 15 mmHg). . . .”

Purification: Recrystallization

Describe procedure in detail. Indicate solvents used (and ratio of mixed solvent systems), amount of recrystallization solvents, and temperature protocol. Describe how crystals are isolated and what they are washed with.

> “The solid is dissolved in 100 mL of hot diethyl ether (30°C) and filtered through a Büchner funnel. The filtrate is allowed to cool to room temperature, and 20 mL of hexanes is added. The solution is cooled at –20°C overnight and the resulting crystals are collected by suction filtration on a Büchner funnel, washed with 50 mL of ice-cold hexanes, and then transferred to a 50-mL, round-bottomed flask and dried overnight at 0.01 mmHg to provide. . . ”

Characterization

Physical properties of the product such as color, appearance, crystal forms, melting point, etc. should be included in the text of the procedure. Comments on the stability of the product to storage, etc. should be provided in a Note.

In a Note, provide data establishing the identity of the product. This will generally include IR, ^{1}H-NMR, and ^{13}C-NMR data, and in some cases UV and MS data. Copies of the proton NMR spectra for the products of each step in the procedure should be submitted showing integration for all resonances. Submission of carbon NMR spectra and other nuclei are encouraged as appropriate.

In the same Note, provide data establishing the purity of the product. This will generally include elemental analysis and/or GC and/or HPLC data. Provide details on equipment and conditions for GC and HPLC analyses.

In procedures involving non-racemic, enantiomerically enriched products, optical rotations should generally be provided, but enantiomeric purity must be determined by another method such as chiral HPLC or GC analysis.

In cases where the product of one step is used without purification in the next step, it is desirable to include a Note describing how a sample of the product can be purified and providing characterization data for the pure material.

Hazard Warnings

Any significant hazards should be indicated in a statement at the beginning of the procedure in italicized type. Efforts should be made to avoid the use of toxic and hazardous solvents and reagents when less hazardous alternatives are available.

Discussion Section

The style and content of the discussion section will depend on the nature of the procedure.

For procedures that provide an improved method for the preparation of an important reagent or synthetic building block, the discussion should focus on the advantages of the new approach and should describe and reference all of the earlier methods used to prepare the title compound.

In the case of procedures that illustrate an important synthetic method or strategy, the discussion section should provide a mini-review on the new methodology. The scope and limitations of the method should be discussed, and it is generally desirable to include a table of examples. Competing methods for accomplishing the same overall transformation should be described and referenced. A brief discussion of mechanism may be included if this is useful for understanding the scope and limitations of the method.

Format

The text of the procedure should be constructed using a standard word processing program, like MS Word, with 14-point Times New Roman font. Chemical structures and schemes should be drawn using the standard ACS drawing parameters (in ChemDraw, the parameters are found in the "ACS Document 1996" option) with a maximum width of 6 inches. The graphics files should be inserted into the document at the correct location and the graphics files should also be submitted separately. All Tables that include structures should be entirely prepared in the graphics (ChemDraw) program and inserted into the word processing file at the appropriate location. Tables that include multiple, separate graphics files prepared in the word processing program will require modification.

Biographies and Photographs of Authors

Photographs and 100-word biographies of all authors should be submitted as separate files at the time of the submission of the procedure. The format of the biographies should be similar to those in the Volume 84 procedures found at the orgsyn.org website. Photographs can be accepted in a number of electronic formats, including tiff and jpeg formats.

HANDLING HAZARDOUS CHEMICALS

A Brief Introduction

General Reference: *Prudent Practices in the Laboratory*; National Academy Press; Washington, DC, 1995.

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless "flammable storage" refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out all operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing at all times.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin contact, and should not be a problem if one follows the admonition “work in a hood and keep chemicals off your hands”. Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no simple correlation between carcinogenicity in animals and in man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices at all times.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves should be worn at all times.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

MSDS (Materials Safety Data Sheets) sheets are available from the suppliers of commercially available reagents, solvents, and other chemical materials; anyone performing an experiment should check these data sheets before initiating an experiment to learn of any specific hazards associated with the chemicals being used in that experiment.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices in the Laboratory* National Academy Press, Washington, D.C. 1996

Effluents from synthetic organic chemistry fall into the following categories:

1. **Gases**
    - 1a. Gaseous materials either used or generated in an organic reaction.
    - 1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
    - 1c. Vapors from volatile reagents, intermediates and products.
2. **Liquids**
    - 2a. Waste solvents and solvent solutions of organic solids (see item 3b).
    - 2b. Aqueous layers from reaction work-up containing volatile organic solvents.
    - 2c. Aqueous waste containing non-volatile organic materials.
    - 2d. Aqueous waste containing inorganic materials.
3. **Solids**
    - 3a. Metal salts and other inorganic materials.
    - 3b. Organic residues (tars) and other unwanted organic materials.
    - 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or

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*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgment of an environmentally aware professional.

academic setting, provision should be made for dealing with the more environmentally offensive categories.

1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
2a. All waste solvents and solvent solutions of organic waste.
2c. Aqueous waste containing dissolved organic material known to be toxic.
2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10–100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

Henry E. Baumgarten
1920–2006

Henry Baumgarten, Professor Emeritus in the Department of Chemistry at the University of Nebraska-Lincoln and a noted organic chemist, died March 12, 2006 at the age of 85. Born in Texas, Henry earned B.A. (1943) and M.A. (1944) degrees in chemistry from Rice University. After service with the U.S. Navy in the Pacific during 1944–1945, he returned to Rice and completed his Ph.D. in chemistry in 1948.

Henry began his career as a research associate at the University of Illinois with Prof. C. S. "Speed" Marvel publishing his first scientific paper describing the emulsion polymerization of 2-alkyl-1,3-butadienes in 1949 in the *Journal of Polymer Science*, volume 4. He moved to the University of Nebraska in 1949, publishing his first independent paper in the *Journal of Organic Chemistry* (1951, volume 16) describing the synthesis of *dl*-3,3,4-trimethylcyclopentanone. His research on structure and reactivity of organic molecules was marked by a focus on amines and strained rings, including pioneering efforts on the synthesis of alpha-lactams, and by an early appreciation for the potential of NMR and mass spectrometry in organic chemistry. He received a Guggenheim fellowship in 1962. He was an editorial board member for *Journal of Organic Chemistry* and *Organic Syntheses*; for the latter series, he was also on the Board of Directors and the Editor of Collective Volume V. His lab manual on organic chemistry, coauthored with Walter Linstromberg, was published through five editions and was well known to both college students and instructors.

Henry was an active birder, serving as both an author and assistant editor for the *Nebraska Bird Review*. He was member and officer in both the Audubon Naturalists' Club and the Nebraska Ornithologists Union. After his retirement, he was active in the Nebraska Academy of Sciences.

Henry remained on the faculty at UNL for nearly forty years, becoming Regents Professor of Chemistry and serving as department chair, President of the UNL Academic Senate, and UNL Vice Chancellor for Research. He was a member of ACS for more than fifty years.

JAMES TAKACS
Lincoln, Nebraska

PREFACE

The chemical literature continues to grow rapidly. Despite challenges, scientists continue to make important advances related to fundamental and applied knowledge that are needed to continuously improve quality of life for a growing world population. With this increased scientific output, which has led to a proliferation of journals and research papers, comes the daunting task of keeping pace with the rapid evolution of scientific methods. A major concern is that scientists will have less and less time to pay attention to details reported in experimental sections of papers; yet vicarious learning from attention to subtle experimental details can make the difference between success and failure in experimental work. This 84th Volume of *Organic Syntheses* continues to emphasize the importance of having available experimentally checked and detailed chemical procedures on which the chemical community can rely and perhaps should emulate. As indicated by Professor Dennis Curran in his preface to Volume 83, continuation of this significant effort was of concern when Professor Jeremiah Freeman retired after 25 years of contributing to and effectively running *Organic Syntheses*, but Professors Rick Danheiser and Chuck Zercher have done an admirable job in the transition. As also indicated by Dennis in the last volume, Jerry's contributions were recognized by the endowment of the "Jeremiah P. Freeman Organic Syntheses Lectureship" at the University of Notre Dame and the inaugural 2005–2006 academic year lecture by Professor K. Barry Sharpless. The 2006–2007 JPFORGSYN lecture was given by Professor Samuel Danishefsky and the 2007–2008 lecture will be presented by Professor Leo Paquette in April, 2008.

Volume 84, with 35 detailed preparations, reflects the expanded efforts of Rick, Chuck, the editorial board and independent submissions from the chemical community. Though not always the main goal of each procedure, the utility of silyl derivatives in organic synthesis is reflected in several preparations including, ***N*****,*****N*****-DIBENZYL-*****N*****-[1-CYCLOHEXYL-3-(TRIMETHYLSILYL)-2-PROPYNYL]-AMINE FROM CYCLOHEXANECARBALDEHYDE, TRIMETHYLSILYLACE-**

TYLENE AND DIBENZYLAMINE, a procedure that also illustrates a very effective catalytic asymmetric reductive amination, **GENERATION OF YNOLATE AND *Z*-SELECTIVE OLEFINATION OF ACYLSILANES: (*Z*)-2-METHYL-3-TRIMETHYLSILYL-2-BUTENOIC ACID** and **SYNTHESIS OF ACYLSILANES FROM MORPHOLINE AMIDES. SYNTHESIS OF 1-(DIMETHYL-(PHENYL)SILYL)PROPAN-1-ONE**, the former of which also describes a useful *Z*-selective oleÞnation.

The value of alkyne chemistry is amply illustrated by the following procedures: **SYNTHESIS OF TERMINAL 1,3-DIYNES VIA SONOGASHIRA COUPLING OF VINYLIDENE CHLORIDE FOLLOWED BY ELIMINATION. PREPARATION OF 1,3-DECADIYNE** and **SYNTHESIS OF YNAMIDES BY *N*-ALKYNYLATION OF AMINE DERIVATIVES. PREPARATION OF *N*-ALLYL-*N*-(METHOXYCARBONYL)-1,3-DECADIYNYLAMINE**. A catalytic *N*-alkynylation is provided in **PRACTICAL SYNTHESIS OF A CHIRAL YNAMIDE: (*R*)-4-PHENYL-3-(2-TRIISOPROPYLSILYLETHYNYL)-OXAZOLIDIN-2-ONE**. More alkyne chemistry is provided in **(*S*)-(+)-NEOMENTHYLDIPHENYLPHOSPHINE IN NICKEL-CATALYZED ASYMMETRIC REDUCTIVE COUPLING OF ALKYNES AND ALDEHYDES: ENANTIOSELECTIVE SYNTHESIS OF ALLYLIC ALCOHOLS AND α-HYDROXY KETONES**, a procedure that also illustrates enantioselective catalysis as does, **SYNTHESIS OF 4-TRIISOPROPYLSILYL-3-BUTYN-2-OL BY ASYMMETRIC TRANSFER HYDROGENATION.** Procedures entitled **PREPARATION OF A TRISAMIDOMOLYBDENUM(VI) PROPYLIDYNE COMPLEX–A HIGHLY ACTIVE CATALYST PRECURSOR FOR ALKYNE METATHESIS** and **PREPARATION OF A CARBAZOLE-BASED MACROCYCLE VIA PRECIPITATION-DRIVEN ALKYNE METATHESIS** illustrate examples of alkyne chemistry and the emerging importance of alkyne metathesis reactions. Utilization of alkynes for preparation of highly substituted furans is illustrated by **ELECTROPHILIC CYCLIZATION WITH *N*-IODOSUCCINIMIDE: PREPARATION OF 5-(4-BROMOPHENYL)-3-IODO-2-(4-METHYL-PHENYL)FURAN. PREPARATION OF BENZOCYCLOBUTENONE DERIVATIVES BASED ON AN EFFICIENT GENERATION OF BENZYNES** provides an example of the versatility of new benzyne chemistry.

Asymmetric transformations, especially catalytic processes, are represented by several of the preparations already mentioned as well as the preparation of chiral catalyst precursors as in **PREPARATION OF (η^5-(*S*)-2-(4-METHYLETHYL) OXAZOLINYLCYCLOPENTADIENYL)-(η^4-TETRAPHENYLCYCLO BUTADIENE)COBALT** and catalysts themselves including **PREPARATION OF THE COP CATALYSTS: [(*S*)-COP-OAc]$_2$, [(*S*)-COP-Cl]$_2$, AND (*S*)-COP-hfacac.** Various other metal-catalyzed processes include the use of copper with a zirconium reagent in **COPPER(I) IODIDE DIMETHYL SULFIDE CATALYZED ADDITION OF A VINYLZIRCONIUM REAGENT. PREPARATION OF 4-PHENYL-5(*E*)-DECEN-2-ONE**, palladium for arylation of an aniline in **SELECTIVE Pd-CATALYZED AMINATIONS ON CHLORO IODOPYRIDINES: SYNTHESIS OF ETHYL 4-[(6-CHLOROPYRIDIN-3-YL)AMINO]BENZOATE**, and gold/silver catalysis in **HIGHLY EFFICIENT ADDITION OF ACTIVATED METHYLENE COMPOUNDS TO ALKENES CATALYZED BY GOLD AND SILVER**. Catalytic desymmetrization processes are becoming extremely useful, as demonstrated by **CHIRAL LITHIUM AMIDE BASE DESYMMETRIZATION OF A RING FUSED IMIDE: FORMATION OF (3a*S*,7a*S*)-2-[2-(3,4-DIMETHOXYPHENYL)-ETHYL]-1,3-DIOXO-OCTAHYDRO-ISOINDOLE-3a-CARBOXYLIC ACID METHYL ESTER**.

Functional group introduction, interconversion and elaboration are at the heart of organic synthesis. Several examples are included in the preparations already listed and more selective processes are described in **A XANTHATE-TRANSFER APPROACH TO α-TRIFLUORO-METHYLAMINES[2-(*N*-ACETYLAMINO)-4,4-DIMETHOXY-1,1,1-TRIFLUOROBUTANE]; THIONATION: GlcNAc-THIAZOLINE TRIACETATE {(3a*R*,5*R*,6*S*,7*R*,7a*R*)-5-ACETOXYMETHYL-6,7-DIACETOXY-2-METHYL-5,6,7,7a-TETRAHYDRO-3a*H*-PYRANO-[3,2-*d*]THIAZOLE}; PREPARATION OF *N*-*p*-TOLYLSULFONYL-(*E*)-1-PHENYLETHYLIDENEIMINE; 1,3-DICHLOROACETONE AS A CYCLOPROPANONE EQUIVALENT: 5-OXASPIRO-[3.4]OCTAN-1-ONE; A PRACTICAL PROCEDURE FOR CARBONYL α-OXIDATION: SYNTHESIS OF (2-BENZOYLOXY)-1,4-CYCLOHEXANEDIONE *MONO*-ETHYLENE KETAL; PREPARATION OF SUBSTITUTED 5-AZAINDOLES: METHYL 4-CHLORO-1*H*-PYRROLO[3,2-*C*]PYRIDINE-2-CARBOXYLATE; SYNTHESIS OF MULTIFUNCTIONALIZED KETONES THROUGH THE FUKUYAMA COUPLING REACTION CATALYZED BY**

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Functionalization along with homologation or chain extension processes are represented by **STEREOSELECTIVE ISOPRENOID CHAIN EXTENSION WITH ACETOACETATE DIANION: (*E*, *E*, *E*)-GERANYLGERANIOL FROM (*E*, *E*)-FARNESOL** and **SYNTHESIS OF AN *ANTI*-α-AMINO EPOXIDE BY ONE-CARBON HOMOLOGATION OF AN α-AMINO ESTER: (*2S,3S*)-1,2-EPOXY-3-(BOC-AMINO)-4-PHENYLBUTANE**. A number of procedures already listed include coupling processes, and another aryl coupling is represented by **1-(4-ACETYLPHENYL)-2-PHENYLETHANE FROM POTASSIUM 2-PHENETHYLTRIFLUOROBORATE AND 4-BROMOACETOPHENONE**.

Protecting group chemistry is also an important component of organic chemistry. A new, highly improved method for introduction of the commonly used MOM group is described in **SYNTHESIS OF ALPHA-HALO ETHERS FROM SYMMETRIC ACETALS AND *in situ* METHOXYMETHYLATION OF AN ALCOHOL**. A distinct advantage of this method is the avoidance of conditions that would generate the more toxic dichloromethyl ethers. A facile introduction of a benzyl protecting group is reported in **PROTECTION OF ALCOHOLS USING 2-BENZYLOXY-1-METHYLPYRIDINIUM**

TRIFLUOROMETHANE SULFONATE: METHYL (*R*)-(−)-3-BENZYLOXY-2-METHYL PROPANOATE. Selective monoprotection of a symmetrical diamine is described in **MONOCARBAMATE PROTECTION OF ALIPHATIC DIAMINES USING ALKYL PHENYL CARBONATES**.

Again, because of the success of Organic Syntheses, Inc., members of the Organic Division of the ACS and other professional chemistry organizations around the world will receive a free bound copy of this volume. Hopefully, even before receiving your copy, you will have already accessed and utilized some of the procedures through the free website "orgsyn.org". The website and free copies of volumes are just part of the service that the corporation provides to our profession. The web site also includes forms for submission of proposed procedures along with details for submission of the procedures themselves. The editorial board is especially interested in encouraging an expansion of the breadth of procedures to interdisciplinary areas and description of new methodologies. Thus, independent proposals are encouraged.

I want to formally thank the Board of Editors that elected me eight years ago. It has been an honor and a privilege to work with such a prestigious group of dedicated scientists who care so much for our profession. Special thanks are also extended to Jerry Freeman for his constant support and enthusiasm, to current editorial colleagues for inspirational discussions and positive example related to the importance of details and versatility, to Rick and Chuck for their tremendous dedication of time and talent and heartfelt thanks to the organic chemistry community for continuing to work so hard, thereby demonstrating their genuine interest and enthusiasm for learning. I consider every day that I learn something a good day and, indeed, every interaction with Organic Syntheses was a learning experience that provided me many good days. This alone is ample compensation to those of us on the editorial board, but we also appreciate the excellent dinners and related social interactions with our colleagues the evenings after the board meetings. I want to thank my family again for their patience while Dad was doing more "homework". Finally, I thank the University of Notre Dame and the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Jena, Germany, for kind support of a sabbatical during the Spring of 2007, when much of this volume was edited.

MARVIN J. MILLER
Volume Editor

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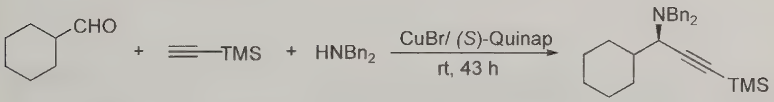

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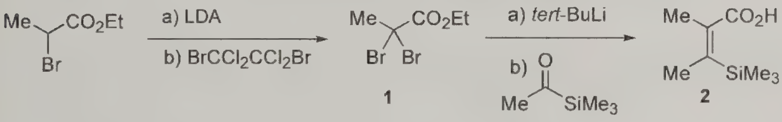

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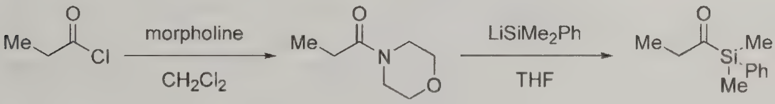

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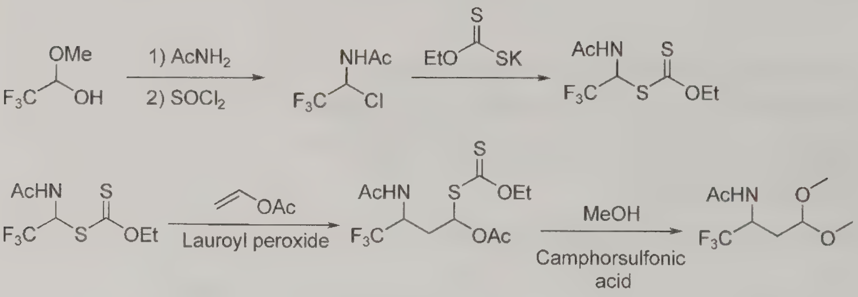

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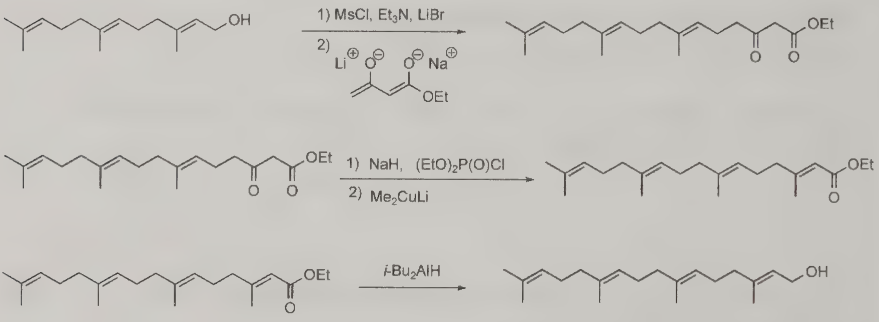

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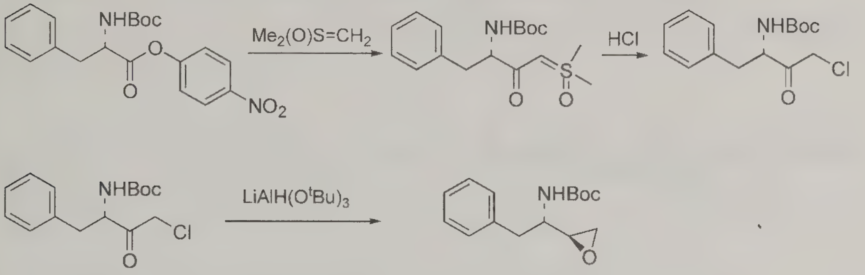

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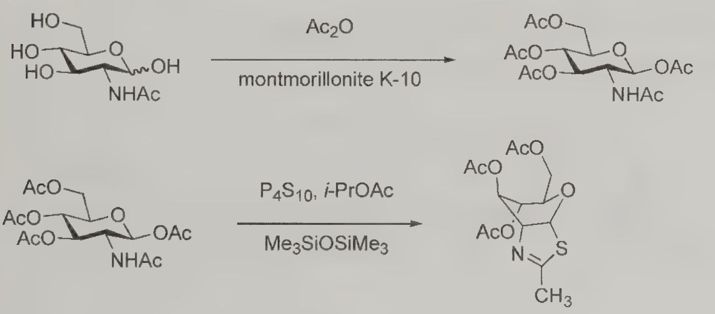

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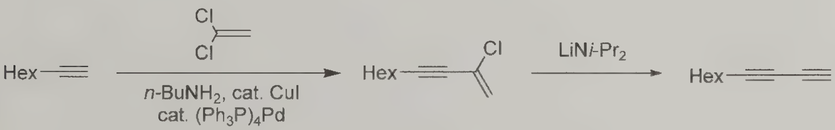

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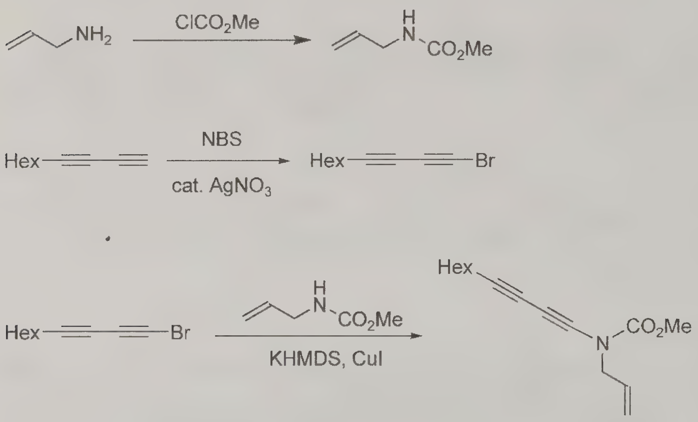

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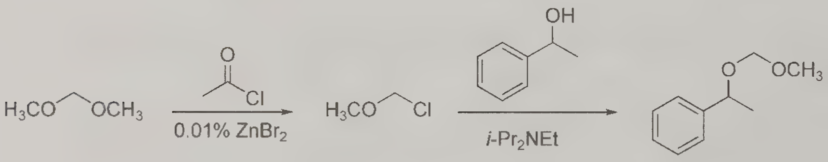

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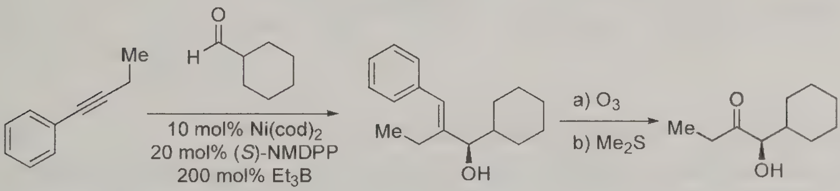

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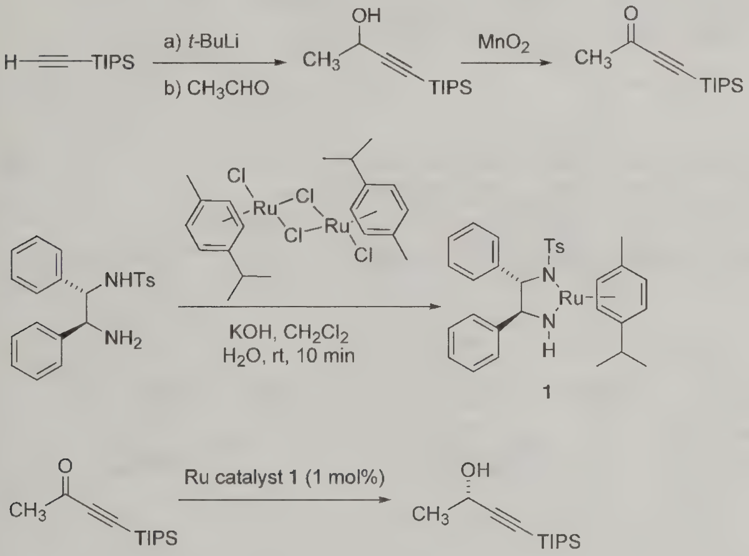

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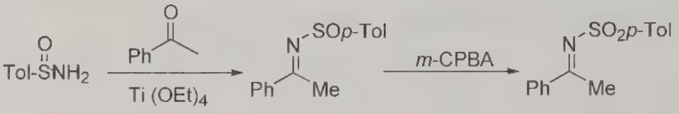

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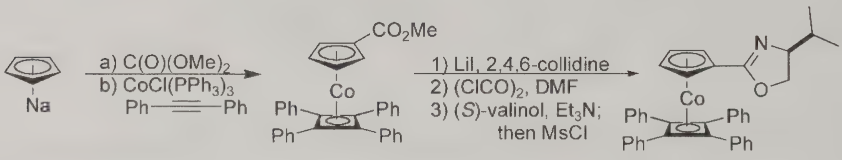

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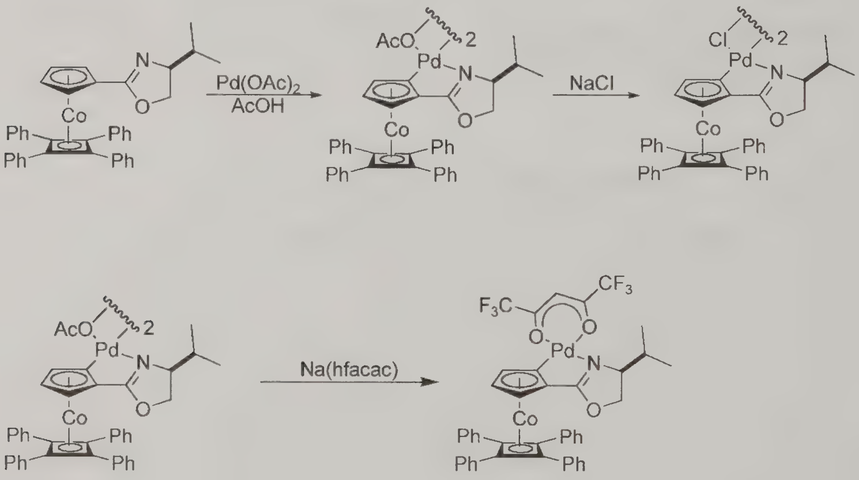

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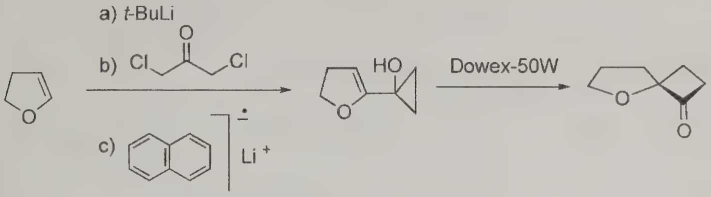

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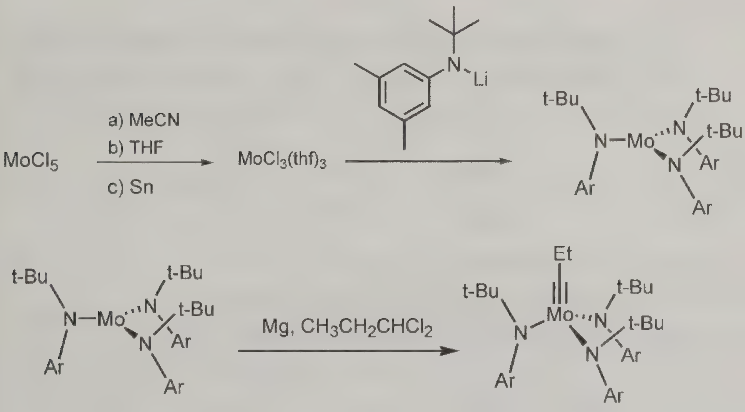

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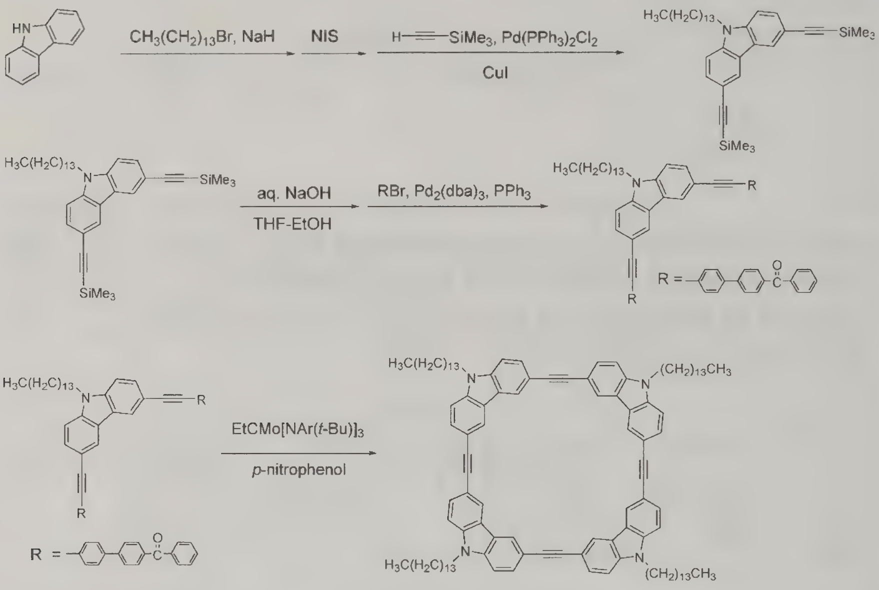

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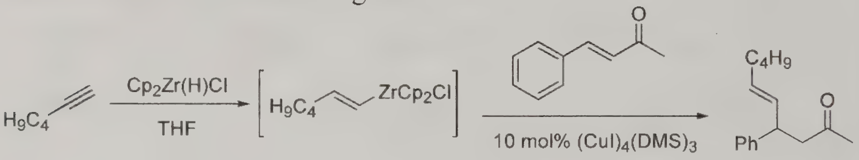

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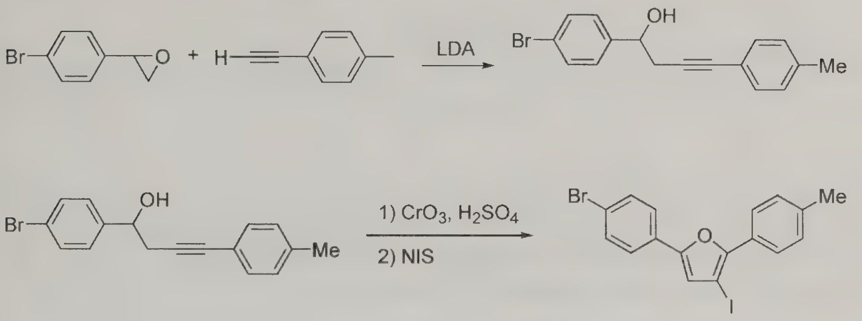

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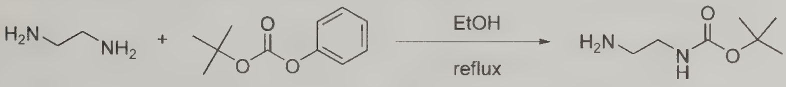

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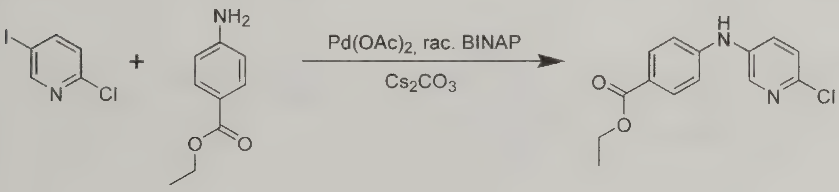

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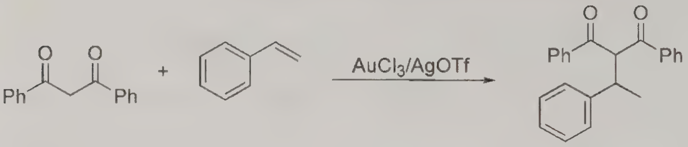

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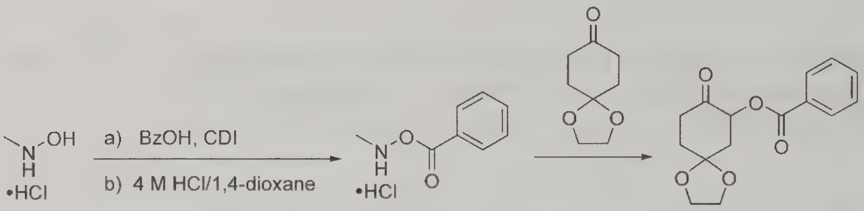

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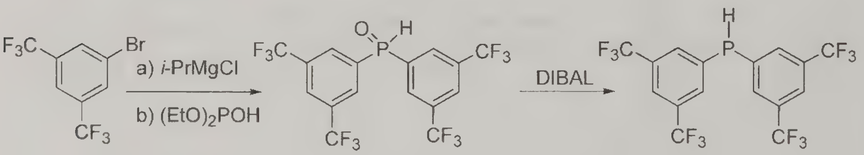

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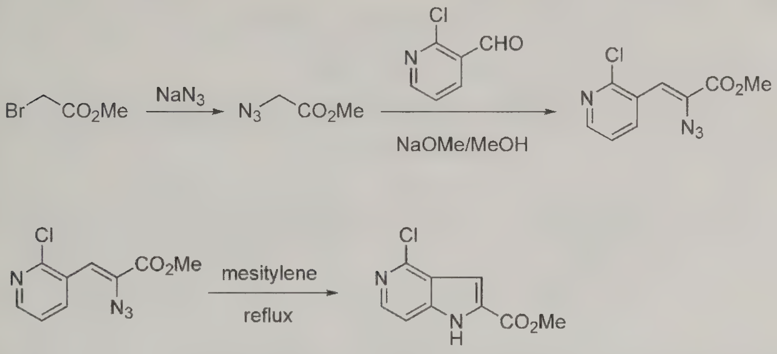

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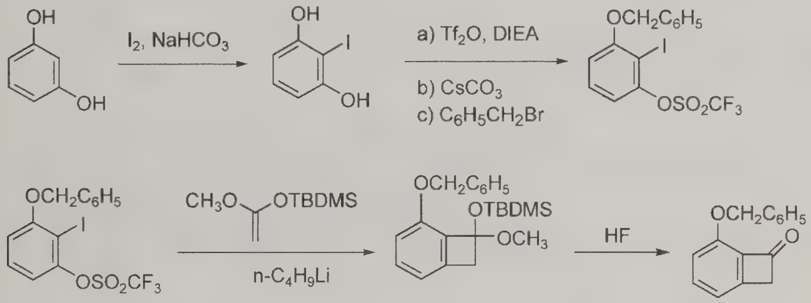

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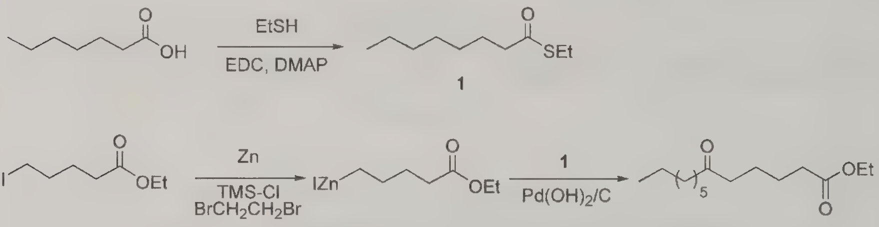

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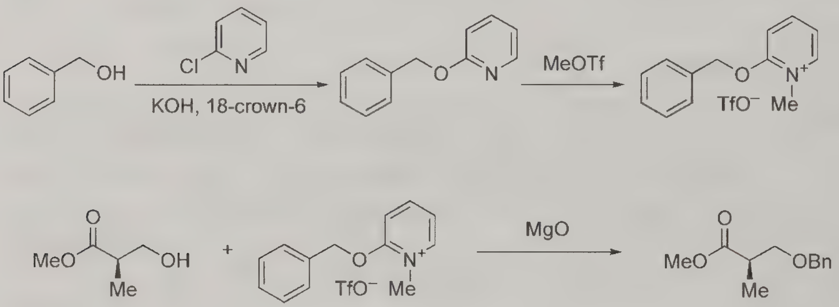

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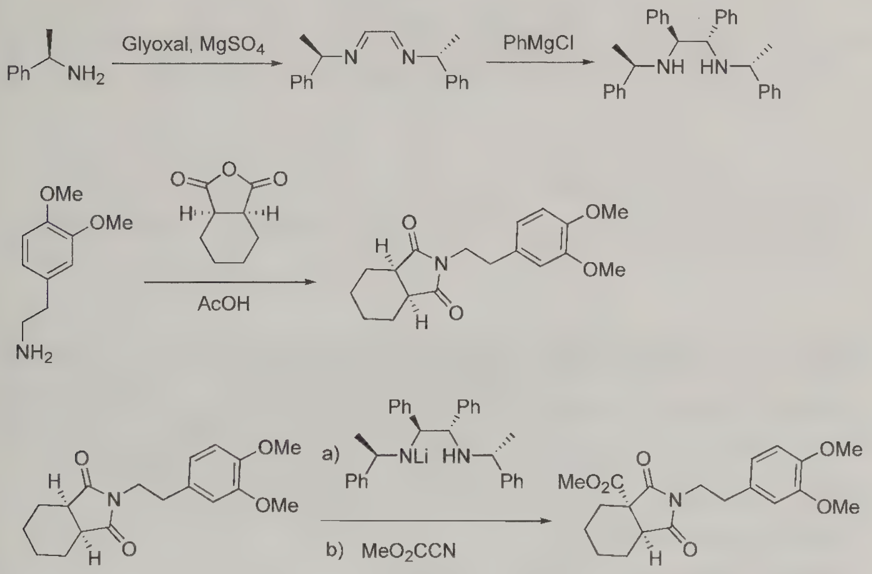

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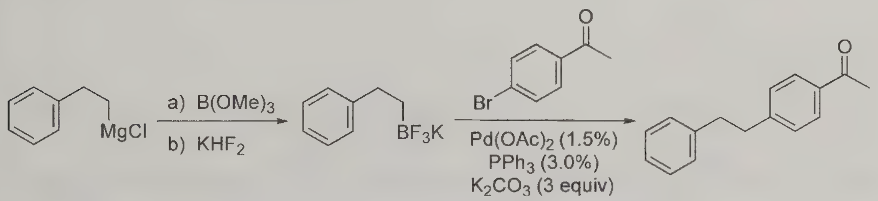

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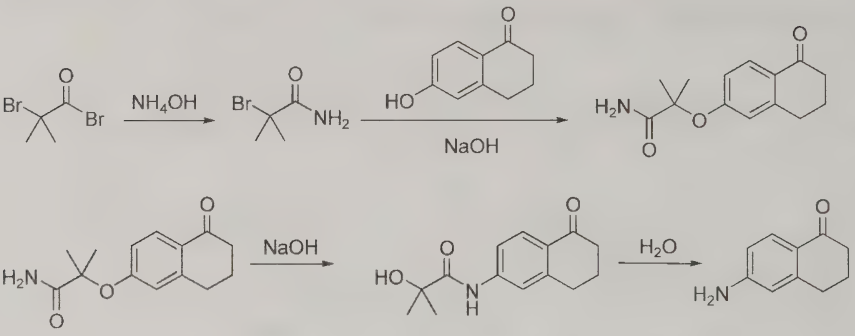

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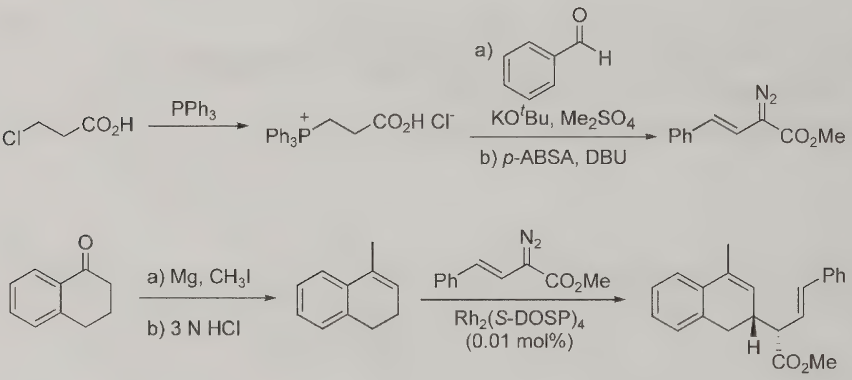

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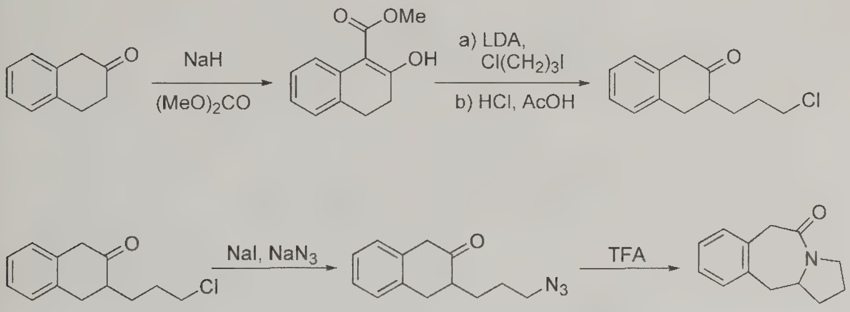

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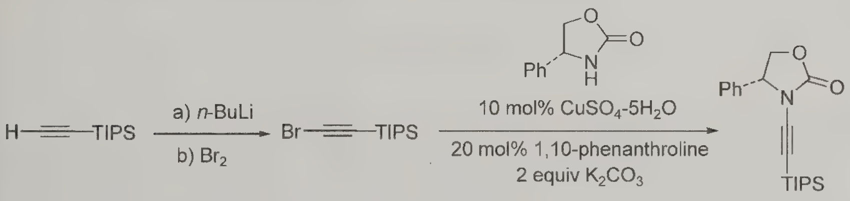

ERRATA

FACILE SYNTHESES OF AMINOCYCLOPROPANES: *N,N*-DIBENZYL-*N*-(2-ETHENYLCYCLOPROPYL)AMINE 368
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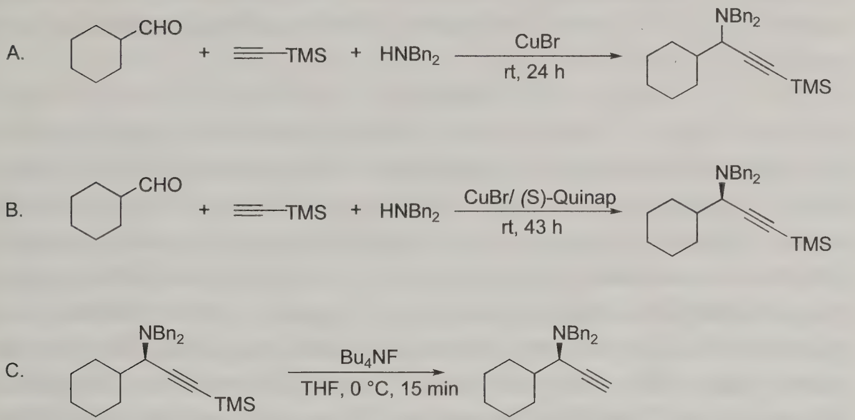
N,N-DIBENZYL-*N*-[1-CYCLOHEXYL-3-(TRIMETHYLSILYL)-2-PROPYNYL]-AMINE FROM CYCLOHEXANECARBALDEHYDE, TRIMETHYLSILYLACETYLENE AND DIBENZYLAMINE



Submitted by Nina Gommermann and Paul Knochel.[1]
Checked by Jason C. Rech and Jonathan A. Ellman.

1. Procedure

A. *(±)-N,N-Dibenzyl-N-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine.* A 100-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum is flame-dried under vacuum (5×10^{-2} mbar), cooled to rt, flushed with argon and charged with copper(I) bromide (143 mg, 1.0 mmol) (Note 1). The flask is evacuated (5×10^{-2} mbar) for 15 min, flushed with argon and charged with dry toluene (40 mL) (Note 2) giving a white suspension. Molecular sieves 4 Å (10 g) (Note 3) is added under a flow of argon. Trimethylsilylacetylene (1.96 g, 2.85 mL, 20.0 mmol) (Note 4) followed by cyclohexanecarbaldehyde (2.24 g, 2.42 mL, 20.0 mmol) (Note 5) are added via syringe (Note 6) in one portion. Dibenzylamine (3.95 g, 3.87 mL, 20.0 mmol) (Note 7) is added during 5 min via syringe. During the addition, the solution becomes clear and turns green at the end of addition. The reaction is slightly exothermic during the addition of dibenzylamine, and subsequently turns milky again. The reaction mixture is stirred for 24 h. After this time, GC-analysis (Note 8) shows more than 96% conversion to

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the desired product. The solution is filtered (Note 9), and the molecular sieves 4 Å are washed with diethyl ether (150 mL). The solution is concentrated by rotary evaporation (55 °C, 760 mmHg, then 38 mmHg). The resulting light green oil is purified by column chromatography (Note 10) affording *N,N*-dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine (6.86 g, 17.6 mmol) as a clear, colorless oil which solidifies upon standing at rt (88%) (Note 11).

B. *(R)-(+)-N,N-Dibenzyl-N-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine.* A 25-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum is flame-dried under vacuum (5 x 10^{-2} mbar), cooled to rt, flushed with argon and charged with copper(I) bromide (21.5 mg, 0.150 mmol) (Note 1) and (*S*)-Quinap (72.5 mg, 0.165 mmol) (Note 12). The flask is evacuated (5 x 10^{-2} mbar) for 15 min, flushed with argon and charged with dry toluene (9 mL) (Note 2) giving a yellow solution with white particles. The mixture is stirred for 30 min at rt, during this time, the solution turns milky. Molecular sieves 4 Å (1.5 g) (Note 3) are added under a flow of argon. Trimethylsilylacetylene (295 mg, 0.43 mL, 3.0 mmol) (Note 4) followed by cyclohexanecarbaldehyde (337 mg, 0.36 mL, 3.0 mmol) (Note 5) are added via syringe (Note 6) in one portion. Dibenzylamine (592 mg, 0.58 mL, 3.0 mmol) (Note 7) is added during one minute via syringe. The suspension is stirred for 43 h at rt, after which time GC-analysis (Note 8) shows more than 96% conversion to the desired product. The solution is filtered (Note 9) and the molecular sieves 4 Å are washed with diethyl ether (50 mL). The solution is concentrated by rotary evaporation (55 °C, 760 mmHg, then 38 mmHg). The resulting yellow oil is dissolved in pentane:diethyl ether (99:1) and filtered from the precipitated catalyst (Note 13). The clear filtrate is subjected to column chromatographic purification (Note 14) affording (*R*)-(+)-*N,N*-dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine (1.07 g, 2.7 mmol) as a clear, colorless oil which solidifies upon standing at rt (91%, 95 % ee) (Note 15).

C. *(R)-(+)-N,N-Dibenzyl-N-(1-cyclohexyl-2-propynyl)-amine.* (*R*)-(+)-*N,N*-Dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine (390 mg, 1.00 mmol), placed in a 25-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, is dissolved in dry THF (5 mL) (Note 16). The solution is cooled to 0 °C for 10 min and Bu_4NF (0.30 mmol, 0.30 mL, 1 M solution in THF) (Note 17, 18) is added dropwise. During the addition, the solution turns slightly yellow. After 15 min, GC analysis (Note 8) shows full conversion. The reaction mixture is quenched with water (30 mL), and the aqueous phase is extracted with diethyl ether (3 x 40 mL). The combined organic fractions are dried over Na_2SO_4 (Note 19) and concentrated by rotary evaporation (55 °C, 760 mmHg, then 38 mmHg). The resulting light yellow oil is purified by column chromatography (Note 20) affording *N*,*N*-dibenzyl-N-(1-cyclohexyl-2-propynyl)-amine (307 mg, 0.97 mmol) as a clear, colorless oil. (97%) (Note 21).

2. Notes

1. CuBr was prepared as described by Taylor:[2] $CuBr_2$ (5.00 g, 22.4 mmol) was placed in a 100-mL round bottomed flask equipped with a magnetic stirring bar and dissolved in water (5 mL). A freshly prepared solution of Na_2SO_3 (3.80 g, 30.1 mmol) in water (25 mL) was added slowly via an addition funnel during 10 min. The initially dark brown mixture turned white and rapidly deposited a white precipitate of CuBr. After the addition was complete, the mixture was stirred for an additional 15 min. Afterwards, the suspension was poured into water (400 mL) which contained Na_2SO_3 (0.50 g) and concentrated hydrochloric acid (1 mL). The mixture was stirred vigorously for 10 min, after which the CuBr was allowed to settle. The supernatant liquid was decanted and the precipitate was transferred to a sintered-glass filter (pore size P4; 75 mL) with diluted sulfuric acid (100 mL, 0.1 M) to prevent oxidation. For the transfer, as well as for the following washing steps, it was ensured that liquid covered the precipitate at all times. With application of gentle suction (375 mmHg), the precipitate was washed with glacial acetic acid (4 x 15 mL), absolute ethanol (3 x 15 mL) and anhydrous diethyl ether (6 x 10 mL). The white crystalline CuBr was immediately transferred to a 50-mL Schlenk flask and dried under vacuum (4×10^{-2} mmHg). CuBr (3.08 g, 21.5 mmol, 96%) was obtained as a white solid and stored under argon, but the solid can be handled routinely in air.

2. Toluene was dried by alumina column (checkers) or dried by distillation under argon from sodium (submitters).

3. Molecular sieves 4 Å, 8 to 12 mesh, were obtained from Acros Organics and used as obtained.

4. Trimethylsilylacetylene was purchased from Lancaster (checkers) or obtained as a generous gift from Wacker Chemie GmbH, Burghausen (submitters), and used as obtained.

5. Cyclohexanecarbaldehyde (98%) was obtained from Aldrich and freshly distilled under reduced pressure (24 mmHg) before use. Reduced yields (65–80%), but not reduced enantioselectivities, were observed when aged starting materials were employed in this procedure.

6. Although the liquid starting materials were transferred via syringe, weighing of the compounds in the syringes instead of measuring the volumes was found to be advantageous. Especially for the smaller scale of the reaction in presence of the chiral ligand (Procedure B), yields were found to be more reliable when the amounts of starting materials were determined by weighing. Therefore, the use of the given mass-values instead of volumes is strongly recommended.

7. Dibenzylamine (98%) was obtained from Acros Organics and freshly distilled under reduced pressure (0.04 mmHg) before use.

8. GC-analysis was carried out using a Hewlett&Packard 5890 Series 2 machine equipped with a HP Ultra-2.5 %-phenylmethylpolysiloxane column (12m x 0.2 mm x 0.33 μm). Oven program for GC-Analysis: Starting temperature, 90 °C for 1 min; heating to 250 °C by a rate of 50 °C per min; 8 min at 250 °C. Retention time of *N*,*N*-Dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine: 7.34 min. The reaction was monitored by the disappearance of the enamine (retention time: 5.83 min).

9. A glass filter with pore size P3 and a volume of 75 mL was used. Filtration was carried out under reduced pressure (300 mmHg).

10. The oil is taken up in 20 mL of the solvent mixture (pentane/diethyl ether, 99:1) and applied to a 5-cm diameter column packed with 200 g Merck silicagel 60 mesh (0.063–0.200 mm), $R_f = 0.35$ (TLC, aluminium sheets, Silica gel 60 F254, obtained from Merck). Approximately 1.5 L of the solvent mixture is used.

11. The submitters reported yields ranging from 6.97–7.01g (88–89%). Spectral data are as follows: checkers mp 68–70 °C, submitters mp 81–82 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.28 (s, 9 H). 0.67–0.89 (m, 2 H), 1.01–1.28 (m, 3 H), 1.52–1.71 (m, 4 H), 1.96 (m, 1H), 2.27 (m, 1 H), 3.01 (d, J = 10.5 Hz, 1 H), 3.34 (d, J = 13.8 Hz, 2 H), 3.78 (d, J = 13.8 Hz, 2 H), 7.19–7.23 (m, 2 H), 7.26–7.34 (m, 4 H), 7.37–7.45 (m, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 0.5, 25.9, 26.1, 26.6, 30.2, 31.2, 39.4, 54.8, 58.5, 90.1, 103.5, 126.8, 128.2, 128.8, 139.8. MS (70 eV, EI): 307 (27), 306 (M^+–c-Hex, 100), 91 (34). HRMS (EI): Calcd. for $C_{26}H_{36}NSi$ [M+H]: 390.2617, found: 390.2628. IR (film): 2924, 2850, 2160, 1494, 1450, 1249, 1004, 841, 746,

698 cm^{-1}. Anal Calcd. for $C_{26}H_{35}NSi$: C: 80.14, H: 9.05, N: 3.59, Found: C: 79.98, H: 8.82, N: 3.79.

12. (S)-Quinap was obtained from Strem Chemicals, Inc. and used as obtained.

13. The oil was mixed with approximately 5 mL of the solvent mixture (pentane/diethyl ether, 99:1) and a light yellow precipitate was formed. The solid was collected by filtration and washed with the solvent mixture (10 mL).

14. Column chromatography was carried out on a 2.5-cm diameter column packed with 50 g Merck silica gel 60 mesh (0.063–0.200 mm) using pentane/diethyl ether, 99:1 as eluent, (R_f = 0.35, TLC aluminum sheets, Silica gel 60 F254, obtained from Merck). Approximately 0.5 L of the solvent mixture is used.

15. The submitters report yields in the range of 1.02–1.04g (88–89%, 95% ee). The enantiomeric excess was determined by HPLC analysis using a Chiracel OD-H column and n-heptane as the eluent after deprotection to form the desilylated derivative (see procedure C), retention times: 36.6 min (*S*), 41.9 min (*R*) (submitters). The enantiomeric excess can also be determined using a Chiracel OD column with hexane as the eluent, retention times: 7.45 min (*S*), 7.89 min (*R*) (checkers). Analytical data: $[\alpha]_D^{20}$ = +168 (c = 1.00, $CHCl_3$) (checkers). The purity of the product was established by ^{1}H-NMR analysis to be >98 %, showing the same data as reported in Note 10.

16. THF was dried by alumina column (checkers) or by distillation from sodium/benzophenone under nitrogen (submitters).

17. Bu_4NF was obtained as a 1M solution in THF from Alfa Aesar and used as obtained.

18. The use of only 0.4 equiv. of Bu_4NF for the cleavage of a TMS-group from acetylenes has been reported by Nishikawa.[3]

19. Na_2SO_4 was obtained from Acros Organics and used as obtained.

20. Column chromatography was carried out on a 2.5-cm diameter column packed with 20 g Merck silicagel 60 mesh (0.063–0.200 mm) using pentane/diethyl ether, 99:1 as eluent, (R_f= 0.30, TLC aluminium sheets, Silica gel 60 F254, obtained from Merck).

21. The submitters reported a yield of 307 mg (99%). Spectral data as follows: $[\alpha]_D^{20}$ = +135 (c = 1.10, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.67–0.89 (m, 2 H), 1.01–1.28 (m, 3 H), 1.52–1.71 (m 4 H), 2.00 (m, 1 H), 2.29 (m, 1 H), 2.34 (d, *J* = 2.4 Hz, 1 H), 3.03 (dd, *J* = 10.5, 2.1 Hz, 1 H),

3.37 (d, J = 13.5 Hz, 2 H), 3.81 (d, J = 13.5 Hz, 2 H), 7.18-7.25 (m, 2 H), 7.26–7.35 (m, 4 H), 7.36–7.45 (m, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.9, 26.1, 26.5, 30.2, 31.2, 39.5, 54.8, 57.6, 73.4, 81.0, 126.8, 128.2, 128.8, 139.7. MS (70 eV, EI): 235 (21), 234 (M+–c-Hex, 100), 91 (88). HRMS (EI): Calcd. for $C_{23}H_{28}N$ [M+H]: 318.2222, found: 318.2222. IR (film): 3300, 2923, 2850, 1490, 1450, 745, 698 cm^{-1}. Anal Calcd. for $C_{23}H_{27}N$: C: 87.02, H: 8.57, N: 4.41, Found: C: 86.78, H: 8.63, N: 4.55. The checkers observed that the colorless oil solidifies upon standing: mp 75–76 °C.

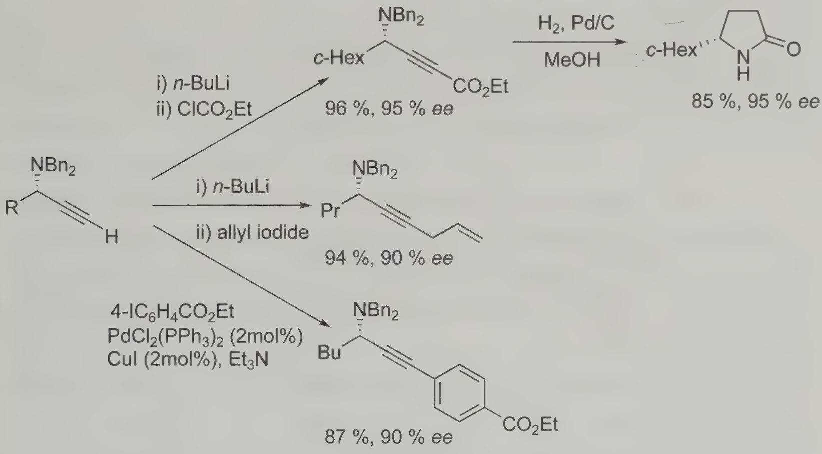
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

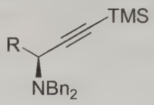
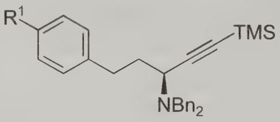
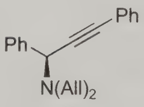
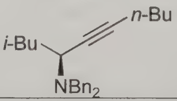
The catalytic, enantioselective formation of new carbon-carbon bonds is an important class of reactions. Especially attractive are multi-component reactions that allow the formation of several bonds including new carbon-carbon bonds in a one-pot procedure. The present procedure describes a convenient method for the preparation of enantiomerically enriched propargylamines in good selectivities and excellent yields.[4] The reaction is catalyzed by the chiral complex formed from Cu(I)Br and commercially available (*R*)- or (*S*)-Quinap[5] (5 mol%). The reaction tolerates a broad range of different aldehydes, including aromatic and heteroaromatic aldehydes, as well as branched and non-branched aliphatic aldehydes. Many types of terminal alkynes are tolerated, but the use of trimethylsilylacetylene provides the best enantiomeric excesses. Furthermore, desilylation to the terminal alkyne potentiates many different transformations (Scheme 1). As the third component, only aliphatic amines can be used; amides or anilines do not undergo the reaction. A major advantage of this reaction is the convenience of the procedure. The reaction is carried out at room temperature with equimolar amounts of starting materials and only 5 mol% of catalyst is necessary, which demonstrates a very atom economical

Scheme 1. Transformations of terminal propargylamines.



reaction.[6] The propargylamines obtained by this procedure are valuable building blocks for organic synthesis. A related synthesis involving imines that uses CuOTf/pybox as the catalytic system is also known, but the reaction is limited to aromatic aldehydes and anilines.[7]

Table 1: Enantiomerically enriched propargylamines obtained by the Cu(I)-Quinap catalyzed three-component coupling of aldehydes, secondary amines and terminal alkynes.

Entry	RCHO	Product of type 3	Yield (%)[a]	%ee[b]
				
1	*n*-Pr	R= n-Pr	88	90
2	*n*-Bu	R= n-Bu	75	90
3	*i*-Bu	R= i-Bu	84	94
4	*i*-Pr	R= i-Pr	84	96
5	*s*-Pent	R= s-Pent	97	98
6	*c*-Pr	R= c-Pr	97	92
7	*c*-Pent	R= c-Pent	97	96
8	3-Benzothiophene	R=3-Benzothiophene	92	82
9	$(C_6H_5)CH=CH$	R= $(C_6H_5)CH=CH$	93	82
10	$(C_6H_5)_2C=CH$	R= $(C_6H_5)_2C=CH$	80	84
				
11	$C_6H_5(CH_2)_2$	R^1= H	76	88
12	4-Br-$C_6H_4(CH_2)_2$	R^1= Br	72	88
13	4-CO_2Et-$C_6H_4(CH_2)_2$	R^1= CO_2Et	83	87
14	Ph		91	70
15	*i*-Bu		85	82

[*a*] Isolated yield of analytically pure product; [*b*] Enantiomeric excess determined by HPLC using Chiracel OD-H column (*n*-heptane : *i*-PrOH).

1. Department of Chemistry, Ludwig-Maximilians-University Munich, Butenandtstr. 5-13, D-81377 München, Germany. Paul.Knochel@cup.uni-muenchen.de
2. Taylor, R. J. *Organocopper Reagents*, *Oxford Univ. Press*, **1994**.
3. Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449.
4. (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; (b) Dube, H.; Gommermann, N.; Knochel. P. *Synthesis* **2004**, 2015; (c) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324.
5. (a) Valk, J. M.; Whitlock, G. A.; Layzell, T. P.; Brown, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2593; (b) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840.
6. (a) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259; (b) Trost, B. M. *Science* **1991**, *254*, 1471.
7. Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Trimethylsilylacetylene: Silane, ethynyltrimethyl-; (1066-54-2)

Cyclohexanecarbaldehyde: Cyclohexanecarboxaldehyde; (2043-61-0)

Dibenzylamine: Benzenemethanamine, *N*-(phenylmethyl)-; (103-49-1)

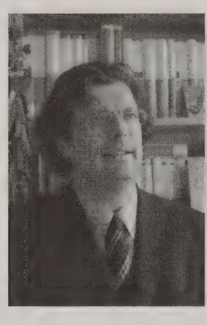
Copper(I) bromide; (7787-70-4)

(*S*)-Quinap: Isoquinoline, 1-[2-(diphenylphosphino)-1-naphthalenyl]-, (1*S*)-; (149341-33-3)

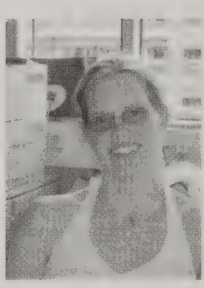
(*R*)-(+)-*N*,*N*-Dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine: Benzenemethanamine, *N*-[(1*R*)-1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-*N*-(phenylmethyl)-; (872357-80-7)

Tetra-*n*-butylammonium fluoride: 1-Butanaminium, *N*,*N*,*N*-tributyl-, fluoride; (429-41-4)

N,*N*-Dibenzyl-N-(1-cyclohexyl-2-propynyl)-amine: Benzenemethanamine, *N*-[(1*R*)-1-cyclohexyl-2-propynyl]-*N*-(phenylmethyl)-; (872357-86-3)



Paul Knochel was born in 1955 in Strasbourg, France. He completed his undergraduate studies at the University of Strasbourg and his Ph.D. at the ETH Zurich with D. Seebach. He spent 4 years with Prof. J.-F. Normant (Paris) and 1 year with Prof. M. F. Semmelhack (Princeton) as a postdoctoral researcher. After professorships at the University of Michigan and the Philipps-Universität (Marburg), he moved to the Ludwig-Maximilians-Universität (Munich) in 1999. His research interests include the development of new synthetic methods with organometallic reagents, new asymmetric catalysts and natural product synthesis.

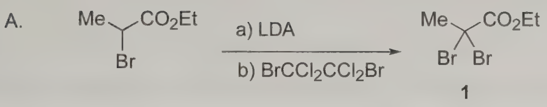


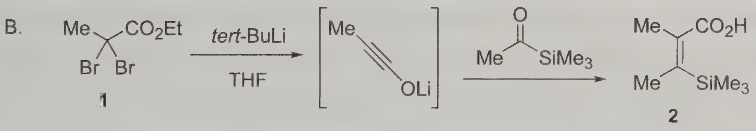
Nina Gommermann was born in 1978 in Kassel, Germany. After undergraduate studies at the Philipps-Universität in Marburg and the Ludwig-Maximilans-Universität (Munich), she joined the group of Prof. Knochel in 2002. She obtained her Ph.D. in 2005 on the enantioselective synthesis of propargylamines and their application in organic synthesis. Since November 2005, she has been a postdoctoral scholar (DAAD fellow) in the group of Prof. David MacMillan at the California Institute of Technology on natural product synthesis.

Jason Rech (born 1977) graduated from Allegheny College with a B.S. degree in chemistry in 1999 where he worked in the laboratory of Professor Martin J. Serra. He worked for the Bayer Corporation in polymer research until entering the Ph.D. program at the University of Pittsburgh in 2000. Under the guidance of Professor Paul E. Floreancig he earned his Ph.D. in 2005 and is currently pursuing postdoctoral research with Professor Jonathan A. Ellman at the University of California, Berkeley.

GENERATION OF YNOLATE AND *Z*-SELECTIVE OLEFINATION OF ACYLSILANES: (*Z*)-2-METHYL-3-TRIMETHYLSILYL-2-BUTENOIC ACID

((*Z*)-2-Butenoic acid, 2-methyl-3-trimethylsilyl-)





Submitted by Mitsuru Shindo,[1] Kenji Matsumoto,[2] and Kozo Shishido.[2]
Checked by Scott E. Denmark and Brian M. Eklov.

1. Procedure

A. *Ethyl 2,2-dibromopropionate* (**1**).[3] A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar and fitted with a thermocouple temperature probe (Note 1) inserted through an adapter, a rubber septum, and a 100-mL, pressure-equalizing addition funnel fitted with a vacuum adapter which is capped with a rubber septum and the sidearm of which is connected to a vacuum/argon gas line. The flask is flame-dried under reduced pressure and then is maintained under an atmosphere of argon during the course of the reaction. The flask is charged with diisopropylamine (23.0 mL, 164 mmol, 1.1 equiv) (Note 2) and anhydrous THF (350 mL) (Note 3), and then is cooled to –71 °C (internal) in a dry ice/isopropyl alcohol bath (Note 4) while a 1.62 M solution of *n*-butyllithium in hexane (102 mL, 165 mmol, 1.1 equiv) (Note 5) is added through the addition funnel over 10 min. After an additional 16 min, a solution of ethyl 2-bromopropanoate (20.0 mL, 27.8 g, 154 mmol) (Note 6)

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in anhydrous THF (20 mL) is added dropwise through the addition funnel over 18 min (the addition funnel is rinsed with 10 mL of anhydrous THF). After an additional 34 min, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (53.7 g, 165 mmol, 1.1 equiv) (Note 7) in THF (60 mL) is added rapidly in one portion through the addition funnel with vigorous stirring (Note 8). After being stirred in the cold bath for 40 min (Note 9), the mixture is poured into 150 mL of saturated aqueous sodium bicarbonate solution in a 1-L separatory funnel (Note 10) and the mixture is extracted with hexanes (2 x 150 mL). The combined organic layers are washed with 150 mL of water and 150 mL of brine, then are dried over $MgSO_4$ (6 g), filtered under vacuum, and concentrated by rotary evaporation (40 °C, 50–100 mmHg) to afford a dark brown oil. The oil is transferred to a 100-mL, round-bottomed flask equipped with a magnetic stirbar and fitted with a short-path distillation unit. Distillation of the product under reduced pressure using an oil bath affords 36.1 g (90% yield) of ethyl 2,2-dibromopropionate (**1**) as a colorless liquid (71–80 °C / 17 mmHg) (Notes 11, 12) after an approximate 5 g forerun.

*B. (Z)-2-Methyl-3-trimethylsilyl-2-butenoic acid (**2**).*[4] A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar and fitted with a thermocouple temperature probe adapter, a rubber septum, and a pressure-equalizing, 200-mL addition funnel fitted with a vacuum adapter capped with a rubber septum. The side arm of the vacuum adapter is connected to a vacuum/argon gas system. The flask is flame-dried under reduced pressure and then maintained under an atmosphere of argon during the course of the reaction. The thermocouple is inserted through the adapter and the flask is charged with ethyl 2,2-dibromopropionate (**1**, 17.6 g, 68.0 mmol, 1.2 equiv) and anhydrous THF (180 mL) (Note 3). The solution is cooled with stirring to –72 °C (internal) in a dry ice/isopropyl alcohol bath, then a 1.72 M solution of *tert*-butyllithium in pentane (158 mL, 272 mmol, 4.9 equiv) (Note 13) is added dropwise over 67 min through the addition funnel such that the internal temperature is kept below –64 °C (Note 14). The addition funnel is rinsed with 5 mL of THF. The yellow solution is stirred at –72 °C for an additional 110 min (3 h total reaction time), and then the cooling bath is replaced by an ice bath. After being stirred at 2 °C (internal) for 30 min, the ice bath is removed, and the mixture is allowed to warm to room temperature. A solution of acetyltrimethylsilane (6.50 g, 56 mmol, Note 15) in anhydrous THF (15 mL) is added through the addition funnel over 15 min (Note 16). The addition funnel is rinsed with 5 mL of anhydrous THF, and the mixture is stirred for 45 min at room temperature. The reaction mixture is poured onto 1 M aqueous NaOH (120 mL) in a 1-L separatory funnel. The organic phase is separated and the aqueous phase (pH 8) is washed with ethyl acetate (2 x 120 mL). The combined organic extracts are washed with 1 M aqueous sodium hydroxide solution (120 mL) and set aside. The combined aqueous extracts (pH 9) are acidified with 6 M HCl (100 mL) to pH 1. The resulting cloudy suspension is extracted with ethyl acetate (3 x 120 mL). These organic extracts are combined, washed with brine (120 mL), dried over $MgSO_4$ (4 g), filtered through a coarse glass frit and then are concentrated on a rotary evaporator (23 °C, 10 mmHg) to yield 7.64 g of a viscous yellow-orange oil that solidifies upon standing in the freezer (–20 °C) (Note 17). The crude product is transferred to a sublimation chamber (chamber: inside diameter, 57 mm; height, 90 mm; condenser: outside diameter, 27 mm; height 70 mm). The bottom of the chamber is cooled in an ice bath and the apparatus is attached to a vacuum line. The bath is removed once the majority of the volatile materials are evaporated as judged by stabilization of the pressure. When the pressure inside the chamber drops below 0.1 mmHg, the condenser is charged with a dry ice/isopropyl alcohol mixture and the chamber is placed in an oil bath, pre-heated to 40 °C. The sublimate was removed from the cold finger three times to afford 6.12 – 6.60 g (64–69%) of **2** as a white crystalline solid (mp 48.5– 50.5 °C, Note 19).

2. Notes

1. A PFA-coated thermocouple probe, Type K (Omega Engineering, Inc.) was inserted through the septum.

2. Diisopropylamine was purchased from Sigma-Aldrich Company (>98.0%) and was distilled from calcium hydride.

3. Anhydrous THF (>99.5%, stabilizer free) was purchased from

Fischer Scientific and was used as received (Karl Fischer analysis gave < 120 μg/mL).

4. For a small scale (smaller than 500-mL flask), the submitters used a low temperature bath with magnetic stirrer (Tokyo Rikakikai Co., Ltd., PSL-1800).

5. *n*-Butyllithium solution was purchased from Sigma-Aldrich and was titrated by both No-D NMR spectroscopy[5a] and Gilman double titration.[5b]

6. Ethyl 2-bromopropanoate (>98%) was purchased from Tokyo Kasei Kogyo Co. Ltd. (TCI) and was distilled.

7. 1,2-Dibromo-1,1,2,2-tetrachloroethane (98%) was purchased from Alfa-Aesar and was used as received. 1,2-Dibromo-1,1,2,2-tetrafluoroethane (>99.0%, Tokyo Kasei Kogyo Co. Ltd.) is more convenient as a bromination reagent, but is not available in the USA.

8. Addition required approximately 30 sec during which time the temperature rose from –71 °C to –35 °C. If this reagent was added slowly, a significant amount of side products were generated, probably due to self-condensation.

9. The progress of the reaction was monitored by gas chromatography. GC-MS analysis was performed on a JMS-Automass SUN200 instrument equipped with a TC-17 30-m x 0.32-mm x 0.25-μm column under the following conditions: injector temp 250 °C; oven temp 60 °C, 3 min; ramp 8 °C/min; final temp 250 °C; helium gas flow 0.8 mL/min; t_R = 4.56 min (dibromo ester), t_R = 2.13 min (bromo ester). The Checkers did not monitor the reaction, but found that the product could be analyzed by GC-MS (Model HP 5890A GC equipped with an HP 5970 MS detector; column HP-1).

10. A large portion of the aqueous solution froze on contact with the reaction mixture. The frozen material was allowed to thaw before performing the extraction.

11. A single distillation afforded material that was contaminated by the starting bromo ester (which could be detected by NMR spectroscopy) and the brominating agent (1,2-dibromo-1,1,2,2-tetrachloroethane). The latter impurity was difficult to identify by TLC (not UV active and did not readily stain), GC (did not combust nor did it ionize easily), IR (C-Cl stretches were

weak and were obscured by the dibromo ester), or NMR (no protons to observe and the ^{13}C resonance was suppressed by the long relaxation time and the lack of a proton nOe). Combustion analysis proved to be the only reliable method to determine the purity of the distillate. The combustion analysis results clearly demonstrated that the primary distillation did not satisfactorily remove the haloalkane. Both of these impurities were removed by a second distillation (65–67 °C, 9 mmHg) to afford 29.3–29.4 g (74–75%) of analytically pure material. The dibromo ester was a stable compound that can be distilled, purified by silica gel column chromatography, and stored for months in a refrigerator.

12. Physical and spectroscopic properties of **1** are as follows: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.36 (t, 3 H, $J = 7.0$), 2.65 (s, 3 H), 4.34 (q, 2 H, $J = 7.0$). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.7 (q), 37.3, 52.2, 63.7, 166.8. IR (film) cm^{-1}: 1737. EI-MS *m/z*: 260 (M^++2), 258 (M^+). Anal. Calcd for $C_5H_8Br_2O_2$: C, 23.10; H, 3.10; Br, 61.48. Found: C, 22.79; H, 2.91; Br, 61.53.

13. A solution of *tert*-butyllithium in pentane was purchased from Sigma Aldrich Company and was titrated by both No-D NMR spectroscopy[5a] and Gilman double titration.[5b] This lithium-halogen exchange procedure for the preparation of ynolates[6] is suitable for a laboratory scale because of its convenience and simplicity. Reductive lithiation with lithium metal catalyzed by naphthalene was better for larger scale.[7]

14. The exothermicity of the reaction subsided substantially after one half of the alkyllithium reagent was added. Thus, the rate of addition was increased after this point without a concomitant increase in internal temperature.

15. Acetyltrimethylsilane (97%) was purchased from Aldrich Chemical Company and was distilled prior to use (bp 110–116 °C).

16. The reaction of the acylsilane with the lithium ynolate was exothermic and reached a maximum temperature of 39 °C. The addition rate was adjusted to minimize the loss of pentanes from the solution.

17. TLC analysis was performed on Merck silica gel 60 F-254 plates eluting with hexanes/EtOAc, 4:1, $R_f = 0.43$ (visualized with 254 nm UV lamp).

18. The product was obtained in analytically pure form by distillation on a half scale. The submitters reported that distillation of the product on the full scale led to polymerization.

19. Physical and spectroscopic properties of **2** are as follows: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.16 (s, 9 H), 1.90 (q, 3 H, J = 1.0), 1.97 (q, 3 H, J = 1.0), 11.6–12.6 (br s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 0.2, 15.4, 20.4, 136.0, 155.6, 175.1. ^{29}Si-NMR (119 MHz, $CDCl_3$) δ: -5.15. IR (film) cm^{-1}: 2966, 1679. MS (EI) *m/z* 157 (M^+ –Me). Anal. Calcd. for. $C_8H_{16}O_2Si$ C, 55.77; H 9.36. Found: C, 55.78, H. 9.63.

Safety and Waste Disposal Information

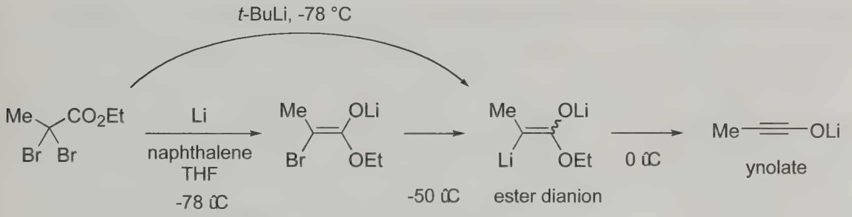
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

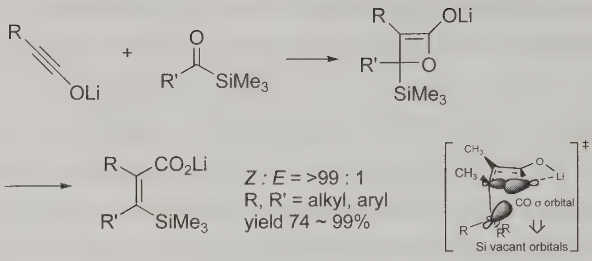
Ynolates[8] are ketene anion equivalents and are expected to act as multifunctional carbanions for ~~the~~ highly reactive ketenes. Although about 10 reports on the syntheses of ynolates have been published, studies on the versatility of ynolates have remained at a rather basic level, probably due to a lack of convenient and general methods for their synthesis. In *Organic Syntheses*, only one report on ynolates has been published.[9]

The procedure described here demonstrates a practical and convenient method for the generation of ynolates, and a (*Z*)-selective olefination of acylsilanes leading to (*Z*)-2-methyl-3-trimethylsilyl-2-butenoic acid.

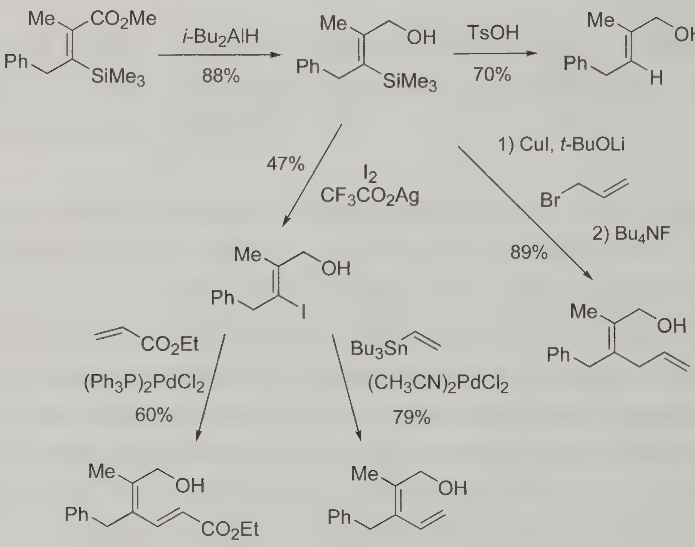
The method for the generation of ynolates involves thermal cleavage of ester dianions derived from α,α-dibromo esters. We have synthesized aliphatic dibromo esters (R = Me, Bu, *i*-Pr, cyclohexyl, *t*-Bu, phenylethyl, trimethylsilyl, etc.) by the method described herein. Aromatic dibromo esters are synthesized via radical bromination. Two procedures for the generation of ester dianions from the dibromo esters have been developed. Herein, lithium-halogen exchange of dibromo esters via *tert*-butyllithium giving the ester dianions is described. This procedure is very convenient, simple and suitable for laboratory scale. In an alternative procedure, the naphthalene-catalyzed reductive lithiation[6] of the dibromo esters with lithium metal is employed. As outlined in the following scheme ~~of~~ for the generation of ynolates using reductive lithiation catalyzed by naphthalene,[10] the dibromo ester reacts with lithium naphthalenide at –78 °C to give an α-bromo ester enolate, which is successively lithiated to form the ester dianion. The dianion is cleaved at 0 °C to generate an ynolate by release of lithium ethoxide.



Vinylsilanes are powerful tools in synthetic organic chemistry. Although olefination of acylsilanes is expected to be a useful method for the preparation of vinylsilanes, few reports on this process have been reported due to the unsuitability of conventional olefination reagents. We have developed a method in which olefination of ketones via ynolates provides α,β-unsaturated carboxylates with good to moderate *E/Z* selectivities.[11] Using acylsilanes as a ketone in this process, however, extremely high *Z*-selectivity is achieved in the synthesis of various substituted vinylsilanes. The *E/Z* selectivity is controlled in the electrocyclic ring-opening of the intermediate β-lactone enolates, prepared by cycloaddition of carbonyl groups with ynolates. In this step, the transition state would be stabilized by the orbital interaction between a breaking C-O s orbital and Si vacant orbitals.[12]



The vinylsilanes produced can be converted into a variety of functionalized multisubstituted alkenes.



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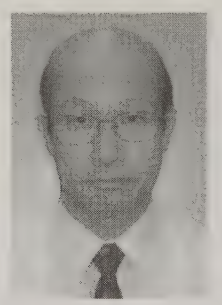
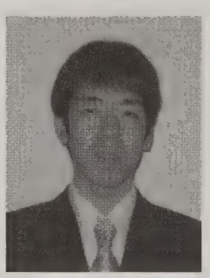
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

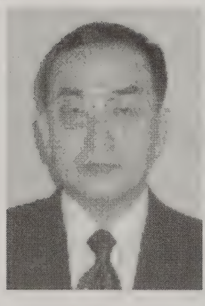
1,2-Dibromo-1,1,2,2-tetrachloroethane; (630-25-1)
Ethyl 2-bromopropanoate: Propanoic acid, 2-bromo-, ethyl ester: (535-11-5)
Ethyl 2,2-dibromopropionate: Propanoic acid, 2,2-dibromo-, ethyl ester; (34757-17-0)
Acetyltrimethylsilane; (13411-48-8)



Mitsuru Shindo was born in Tokyo in 1963. He received his PhD degree at University of Tokyo under the supervision of the late Professor K. Koga. From 1990 until 1996, he was an assistant professor at the laboratory of Professor K. Koga. He spent time in Professor R. A. Holton's group (Florida State University) as a postdoctoral fellow from 1992 until 1994. In 1996, he moved to the University of Tokushima as an associate professor working with Professor K. Shishido. In 2005, he joined the faculty at Kyushu University (Prof. Kanemasa's group) as an associate professor. He is interested in finding new methodologies for synthetic reactions and in the total synthesis of biologically important natural products.



Kenji Matsumoto was born in Hiroshima (Japan) in 1978. He graduated from the University of Tokushima in 2001, where he received his Ph.D. in Organic Chemistry in 2006 under the supervision of Professors Mitsuru Shindo and Kozo Shishido. From 2003 until 2006, he was a research fellow of the Japan Society for the Promotion of Science (JSPS). Since 2006 he has worked as a postdoctoral fellow under the direction of Professor Sergey A. Kozmin at the University of Chicago (USA). He is interested in the development of useful synthetic methods and efficient synthetic strategies.

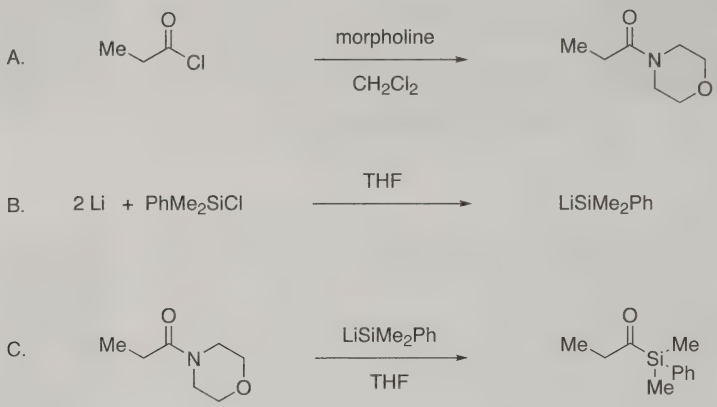


Kozo Shishido received his Ph.D degree from Tohoku University in 1976 under the direction of the late Professor Tetsuji Kametani. After he was appointed as Assistant Professor at Tohoku University, he had postdoctoral fellowships with Professor A. I. Scott (Texas A&M University) and Professor M. E. Jung (UCLA) from 1978 to 1980. He then moved to University of Tokushima as Associate Professor in 1989. Since 1994, he has been a Full Professor at the Graduate School of Pharmaceutical Sciences, University of Tokushima. His main research interests are devoted to total synthesis of biologically active natural products and development of new preparative methods.

Brian Eklov graduated with a B.S. in Chemistry from the University of Michigan in 1998 and completed his Ph.D. thesis in 2005 under the direction of Professor Thomas. R. Hoye at the University of Minnesota. His thesis included discussions of a hybrid computational/ ^{1}H NMR based method for the elucidation of the relative configuration of complex organic molecules, developing the use of non-deuterated solvents for ^{1}H NMR spectroscopy (No-D NMR), and a total synthesis of (+)-gigantecin, a skipped bis-THF acetogenin. He is presently pursuing post-doctoral research with Professor Scott Denmark at the University of Illinois.

SYNTHESIS OF ACYLSILANES FROM MORPHOLINE AMIDES. SYNTHESIS OF 1-(DIMETHYL(PHENYL)SILYL)PROPAN-1-ONE

[Dimethyl(1-oxopropyl)phenylsilane]



Submitted by Robert B. Lettan II, Benjamin C. Milgram, and Karl A. Scheidt.[1]
Checked by Scott E. Denmark and Ramil Y. Baiazitov.

1. Procedure

A. *1-Morpholinopropan-1-one.* A flame-dried, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL addition funnel (capped with a rubber septum), a nitrogen inlet and Teflon-coated thermocouple (Note 1) is charged with 32.9 mL (32.9 g, 378 mmol, 1.1 equiv) of morpholine (Note 2), which is added by syringe to the addition funnel with the stopcock open. Methylene chloride (175 mL) (Note 3) is added by syringe through the same septum and is used to rinse the addition funnel. The stopcock is closed and solution is placed under a positive pressure of nitrogen from a manifold. While stirring the solution, the flask and its contents are cooled in a NaCl/ice bath (internal temperature –8 °C). To the stirred solution is added propanoyl chloride (15.0 mL, 15.9 g, 172 mmol) (Note 4) through the addition funnel over 20 min (Note 5). Following the addition, the mixture is allowed to warm to ambient temperature. The mixture is stirred for 23 h at ambient temperature (Note

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6). Then the solution is diluted with 70 mL of methylene chloride and transferred to a 1-L separatory funnel. The mixture is subsequently washed with 1N HCl (2 x 50 mL), and a mixture of saturated aqueous sodium bicarbonate (25 mL) and brine (50 mL) in a 1-L separatory funnel. The organic phase is dried over 10 g of anhydrous magnesium sulfate, filtered through glass wool, and concentrated by rotary evaporation (10 mmHg) to provide 27.4 g of a colorless liquid. The product is distilled with a short path distillation head (50 mm Vigreaux column) (oil bath temperature 110–120 °C) to afford 21.3 g (86%) of 1-morpholinopropan-1-one as a clear liquid (bp 83–86 °C, 1.1 mmHg) (Notes 7, 8).

B. *Dimethylphenysilyllithium.* This reagent is prepared according to the procedure of Fleming and coworkers.[2] A flame-dried, 300-mL, two-necked, Schlenk flask equipped with a magnetic stirring bar, nitrogen inlet and a rubber septum is charged with 33 cm (45 mg/cm, 1.49 g, 214 mmol, 1.5 equiv) of lithium wire (Note 9) and is filled with nitrogen. Tetrahydrofuran (60 mL, Note 10) is added by syringe through the septum. To the suspension of lithium wire is added chlorodimethylphenylsilane (12.0 mL, 71.5 mmol) (Note 11) by syringe at ambient temperature with stirring (Note 12). Following the addition of chlorodimethylphenylsilane, the reaction flask is tightly sealed and then transferred to a –15 to – 20 °C freezer and is allowed to stand for 59 h. The resulting, purple solution of dimethylphenylsilyllithium in THF is titrated to 0.97 M against phenolphthalein with 0.1 N HCl (Note 13).

C. *1-(Dimethyl(phenyl)silyl)propan-1-one.* A flame-dried, 250-mL, 3-necked, round-bottomed flask, equipped with a magnetic stirring bar, a nitrogen inlet, a Teflon-coated thermocouple and a rubber septum, is charged with of 1-morpholinopropan-1-one (6.0 g, 41.9 mmol) by syringe under a nitrogen atmosphere from a manifold. To the flask is added 45 mL of THF (Note 10) by syringe. The solution is then cooled to –74 °C (internal) with a dry ice/acetone bath and dimethylphenylsilyllithium in THF (0.97 M solution, 52 mL, 50.4 mmol, 1.2 equiv) is added dropwise by syringe over 8 min such that the internal temperature never rises above –60 °C. The purple reaction mixture is stirred for 70 min at –75 °C (Note 14), quenched with 100 mL of saturated aqueous ammonium chloride solution, and then is allowed to warm to ambient temperature. The mixture is diluted with 40 mL of water in a 1-L separatory funnel and is extracted with hexanes (150 mL) and ethyl acetate (2 x 50 mL). The combined organic extracts are washed with saturated aqueous ammonium chloride (50 mL) and brine (100 mL), then are dried over 11 g of anhydrous magnesium sulfate, filtered through glass wool, and concentrated by rotary evaporation under vacuum (10 mm Hg). The residue is further dried by azeotropic evaporation with hexanes (2 x 50 mL, 10 mmHg) to afford 10.0 g of a light-yellow oil. The product is purified by chromatography on silica gel (50 mm column diameter, 150 g silica gel, packed with precooled hexanes (–15 °C)) using a gradient of precooled solvents (hexanes/CH_2Cl_2: 1/0 (350 mL), 10/1 (500 mL), 5/1 (550 mL), 1/1 (450 mL), 0/1 (250 mL), 60 mL fractions) to provide the acylsilane (5.30 g, 66%) as a light yellow oil and 0.63 g (8%) of a less pure fraction. The larger portion was distilled using a 65-mm Vigreaux column (oil bath, 130 °C) to afford 4.73 g (59%) of 1-(dimethyl(phenyl)silyl)propan-1-one as a light-yellow oil (bp 69–72 °C at 0.94 mmHg) (Notes 15, 16, 17).

2. Notes

1. A PFA-coated thermocouple probe, Type K (Omega Engineering, Inc.) was inserted through a teflon thermometer adapter sealed with an O-ring.

2. Morpholine (99+%) was purchased from Sigma-Aldrich Chemical Co., and was used as received.

3. Anhydrous methylene chloride was obtained by passage through a bed of activated alumina.[3]

4. Propanoyl chloride (98%) was purchased from Sigma-Aldrich Chemical Co., and was used as received.

5. The reaction temperature was monitored internally with a thermocouple during addition of propanoyl chloride, such that the temperature never rose above +10 °C. The reaction was very vigorous and a thick suspension rapidly formed which was difficult to stir magnetically. The use of a mechanical stirrer is highly recommended for larger scale runs.

6. The submitters monitored the progress of the reaction by ^1H NMR spectroscopy. A small aliquot of the reaction mixture was removed by syringe and quenched with 1 mL of saturated aqueous NH_4Cl. The mixture was extracted with 3 mL of ethyl acetate. The organic extraction was dried over Na_2SO_4, filtered through glass wool, and concentrated by vacuum. The remaining material was dissolved in $CDCl_3$, and monitored by ^1H NMR. Reaction completion was monitored by observance of product by ^1H NMR analysis.

7. The submitters used the 1-(dimethyl(phenyl)silyl)propan-1-one without purification for the next step. The amide is somewhat volatile and considerable amounts can be lost by extended exposure to high vacuum.

8. The physical properties are as follows: bp 83–86 °C, (1.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (t, J = 7.4 Hz, 3 H), 2.32 (q, J = 7.5 Hz, 2 H), 3.42–3.46 (t, J = 4.9 Hz, 2 H), 3.58–3.62 (m, 2 H), 3.63–3.66 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 9.3, 26.2, 41.8, 45.7, 66.5, 66.9, 172.4. IR (film): 3493, 2977, 2920, 2854, 1644, 1463, 1435, 1380, 1362, 1300, 1274, 1233, 1116, 1069, 1035, 1008, 990, 942, 905 cm $^{-1}$; MS (EI, 70 eV) *m/z* (rel. intensity) 144 (11), 143 [M^+, 98], 128 (131), 114 (21). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.39; H, 9.32; N, 9.66. The submitters found their product to be > 99% pure by GC (Agilent 6890 Series, column: HP-5; 5% phenyl methyl siloxane, 30 m x 320 μm x 0.25 μm); T-program: 70 °C (1.0 min)→285 °C (25 °C/min); 6.03 min retention time) without distillation.

9. The lithium wire (99.9% in mineral oil) was purchased from Sigma-Aldrich Chemical Co., and was pre-washed with pentanes (2 x 30 mL) to remove the oil and was charged in 1–3 mm segments. If larger (5–10 mm) segments were used the reaction took considerably longer time.

10. Anhydrous tetrahydrofuran was obtained by passage through a bed of activated alumina.[3]

11. A moderate heat evolution was noted in the upper regions of the flask where the lithium floated.

12. The reagent was unstable at room temperature and was kept in an ice bath (0 °C) when not stored in the freezer.

13. Chlorodimethylphenylsilane (98%) was purchased from Gelest and was purified by distillation under vacuum through a short path distillation apparatus, topped with a thermometer, and attached to a receiving flask. (bp 75–77 °C (13–15 mmHg).

14. The submitters monitored the progress of the reaction by TLC analysis on silica gel with 20% EtOAc-hexanes as eluent and visualization with potassium permanganate stain. The amide starting material had R_f = 0.14 and the acylsilane product had R_f = 0.62. Silyl impurities could be visualized at R_f = 0.36 and R_f = 0.72.

15. The checkers found that chromatographic purification was necessary to remove the silicon-containing impurities (mostly disilane and disiloxane). However, chromatography with room temperature solvents led to a significant exotherm (and decomposition) when loading the acylsilane

on silica gel (Silicycle Inc. Ultra Pure Silica Gel Silia*Flash*® P60. Grade: 230–400 mesh (40–63 microns), 60 Å, catalog number R12030B, pH=6.9, water content 6.0%). The acylsilane had an $R_f = 0.22$ (hexane/CH_2Cl_2, 1/1, UV, I_2, CAN) and the major impurities had $R_f = 0.43$, 0.63, and 0.68.

16. Analytical and spectral data are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.51 (s, 6 H), 0.92 (t, $J = 7.3$ Hz, 3 H), 2.61 (q, $J = 7.2$ Hz, 2 H), 7.36–7.44 (m, 3 H), 7.54–7.58 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, 6.1, 41.9, 128.1, 129.8, 133.9, 134.6, 246.2. ^{29}Si NMR (60 MHz, $CDCl_3$) δ: –17.01. IR (film) 2972, 2937, 2898, 1644, 1429, 1403, 1373, 1250, 1111, 1032, 834 cm^{-1} MS (EI, 70 eV) *m/z* (rel. intensity) 191 (4), 163 (20), 137 (12), 136 (19), 135 (100), 105 (11). Anal. Calcd for $C_{11}H_{16}OSi$: C, 68.69; H, 8.39. Found: C, 68.52; H, 8.25.

17. A second run on this scale provided 5.46 g (68%) of the acylsilane. The submitters obtained an 85% yield of material that was still contaminated with disilane and disiloxane.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

In the presence of a strong nucleophile, acylsilanes have the ability undergo a Brook rearrangement (1,2-silyl shift from carbon to oxygen), which has a firmly established synthetic utility.[4] This tactic has been used in various umpolung approaches to carbonyl anions[5] by generating nucleophilicity on the normally electrophilic carbonyl carbon. To exploit this reactivity, acylsilanes have been employed in the synthesis of enolsilanes[6] and alcohols[7] in addition to providing direct access to homoenolates upon addition of vinyl or alkynyl organometallic reagents.[8] More recently, acylsilanes that undergo the Brook rearrangement have been utilized in tandem annulation reactions,[9] and new catalytic acyl anion addition reactions have been developed taking advantage of the unique benefits of the resulting acyl anions.[10] More specifically, acylsilanes in our laboratory have been employed as acyl anion equivalents in the presence of catalytic quantities of thiazolium salts (20-30 mol%) to carry out sila-Stetter reactions,[11] tandem one-pot sila-Stetter/Paal-Knoor transformations,[12] and the direct syntheses of α-amino ketones.[13] However, although acylsilanes are useful entities, standard procedures for accessing these compounds have numerous limitations such as low overall efficiency and a reliance on stoichiometric quantities of a transition metal.

There are many synthetic approaches to construct the carbonyl carbon-silicon bond.[14] Unconventional approaches include the conversion of α,α-dibromobenzylsilanes to acylsilanes on silica gel[15] and the hydroboration of silylalkynes.[16] The trapping of deprotonated dithianes with chlorosilanes has been employed for many years, but this strategy always requires the unmasking of the α-silyl dithiane, which is not always compatible with the substrate.[17] Additionally, benzotriazol-1-yl phenoxyalkanes are useful precursors to a variety of acylsilane structures.[18] Not surprisingly, many of these processes are suboptimal because of poor availability of starting materials or their lack of atom economy.[19] α,β-Unsaturated acylsilanes can be prepared either by a Horner-Wadsworth-Emmons reaction of α-(phosphonoacyl)-silanes[20] or the silyl-Wittig rearrangement of allylic alcohols followed by oxidation.[21] Interestingly, the palladium-catalyzed conversion of aryl acid chlorides to aryl acylsilanes has been reported, but this reaction is limited to the trimethylsilyl group and undergoes decarbonylation with electron deficient aromatic systems.[22]

The addition of anionic silyl nucleophiles to acid chlorides is typically the most direct method for the synthesis of acylsilanes, but this method requires at least two equivalents of the silyllithium reagent and suffers largely from the need for a stoichiometric amount of copper(I) cyanide required for the reaction to proceed in high yield.[23] Unfortunately on a preparative scale, this process becomes prohibitive. As an alternate approach, Fleming and coworkers first noted that the addition of silyl anions to amides afforded acylsilanes, but this process was not adequately explored as a method to construct acylsilanes.[24]

Because the direct addition of organometallic reagents to morpholine amides without over-addition is possible,[25] and more economical than the corresponding Weinreb amides, a direct and efficient synthesis of acylsilanes from amides could be developed.[26] The use of the morpholine amide minimizes over-addition of the silyl nucleophile and also provides the highest yields of the amides surveyed.

The extension of this method to the use of aromatic morpholine amides does not yield the desired acylsilanes. Unlike with the alkyl morpholine amides, additions of silyl anions to aromatic amides usually results in a Brook rearrangement, presumably due to stabilization of the resulting carbanion by the aromatic moiety. Surprisingly, this anion subsequently undergoes an α-elimination of the silyloxy substituent and the ensuing carbene either encounters an additional equivalent of the silyllithium species or dimerizes.[27]

The overall process to prepare alkyl substituted acylsilanes from morpholine amides demonstrated in this procedure has been optimized for a preparative scale, avoids the use of transition metals, and tolerates varied alkyl amide structures, including various protecting groups.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

1-Morpholinopropan-1-one: 4-(1-oxopropyl)-morpholine; (30668-14-5)
Morpholine; (110-91-8)
Propanoyl chloride; (79-03-8)
Chlorodimethylphenylsilane; (768-33-2)
1-(Dimethyl(phenyl)silyl)propan-1-one: Dimethyl(1-oxopropyl)phenylsilane; (128084-44-6)

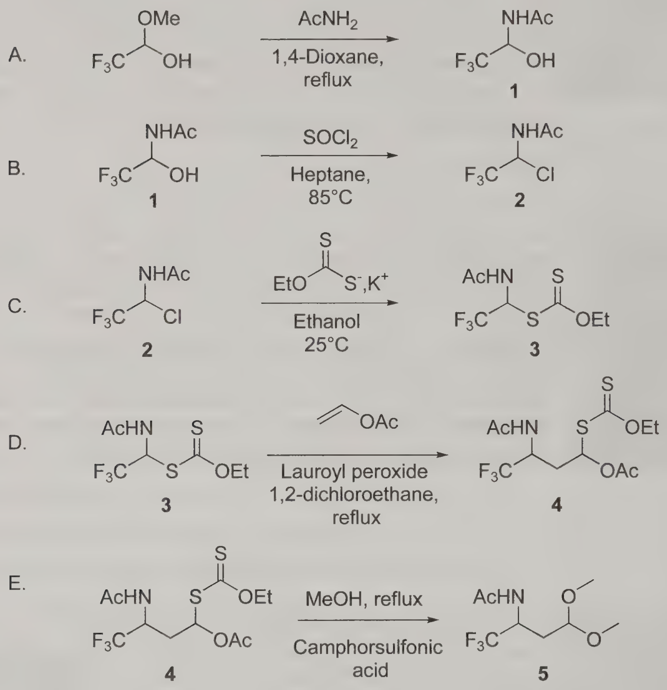
Karl A. Scheidt was born in 1972. He studied chemistry at the University of Notre Dame in the laboratories of Marvin J. Miller. His graduate studies were conducted at Indiana University and the University of Michigan under the direction of William R. Roush. Following his graduate research, he was a NIH Postdoctoral Fellow with David Evans at Harvard University. Since starting his independent career at Northwestern in 2002, his research has focused on the development of new catalytic methods and their applications in organic synthesis. He is the recipient of an Amgen Young Investigator Award, an Abbott Laboratories Young Investigator Award, the Boehringer-Ingelheim New Investigator Award in Organic Chemistry, and a Northwestern University Distinguished Teaching Award.

Robert B. Lettan II was born in Rochester, NY in 1979. He then matriculated at Otterbein College in Columbus, OH, where he received his B. S. in chemistry in 2002. In the fall of 2002, Robert began his doctoral studies at Northwestern University and joined the research group of Professor Karl Scheidt. At Northwestern he has conducted research involving the Lewis base activation of silylalkynes and novel synthetic methods using acylsilanes. In 2006, he was awarded the distinguished Edmund W. Gelewitz award for research and service associated with the Northwestern University Chemistry Department and the surrounding community.

Benjamin C. Milgram was born in Chicago, IL in 1985. He started his undergraduate studies at Northwestern University in 2003. He joined the research group of Karl Scheidt in 2004. During his time in the group he has been awarded a Northwestern University undergraduate fellowship (2004) for work on the synthesis of acylsilanes, a Sigma-Aldrich Research Fellowship (2005) for work on thiazolium catalyzed conjugate additions, and the Katherine Kriegbaum Scholarship for work on the synthesis of isoflavone derivatives (2006).

Ramil Y. Baiazitov graduated with a Diploma in Chemistry from Moscow State University in 1993. As an undergraduate student, he worked under supervision of Prof. Eduard A. Karakhanov on hydroformylation of olefins. After working at a petrochemical company in Ufa, Russia and serving in the Russian Army for almost two years, he worked for three years at the University of Minnesota, Duluth (with Dr. Pavel A. Krasutsky). In Prof. Denmark's group at the University of Illinois, his Ph.D. research is focused on the tandem double intramolecular variant of the [4+2]/[3+2] nitro olefin cycloaddition and its application to total synthesis.

A XANTHATE-TRANSFER APPROACH TO α-TRIFLUOROMETHYLAMINES [2-(*N*-ACETYLAMINO)-4,4-DIMETHOXY-1,1,1-TRIFLUOROBUTANE]



Submitted by Fabien Gagosz and Samir Z. Zard.[1]
Checked by Daniel Laurich and Alois Fürstner.

1. Procedure

A. *N-(2,2,2-Trifluoro-1-hydroxyethyl)-acetamide* (**1**). A 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stir bar and fitted with a glass stopper and a condenser, is charged with 2,2,2-trifluoro-1-methoxyethanol (14.75 g, 102 mmol) (Note 1), acetamide (6.0 g, 102 mmol) (Note 1) and 1,4-dioxane (100 mL) (Note 2). The resulting solution is heated to reflux and stirred in an oil bath under argon for 2 h. The reaction mixture is then cooled to ambient temperature and transferred to a single-necked flask. The solvent is evaporated under reduced pressure and the residue dried

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under vacuum (25 °C, 1 mmHg) for 1 h to give 16.8 g of a colorless solid residue. This product is dissolved in *tert*-butyl methyl ether (20 mL) in a one-necked, round-bottomed flask. Silica gel (10 g) is added to the solution and the solvent is evaporated under reduced pressure (Note 3). The resulting adsorbate is added on top of a silica gel column (approximately 180 g), which is eluted with hexanes/ethyl acetate (3:2). The fractions containing the product are combined and evaporated to give *N*-(2,2,2-trifluoro-1-hydroxyethyl)acetamide (**1**) as a colorless solid (8.98 g, 56%) (Notes 4, 5).

B. *N-1-(Chloro-2,2,2-trifluoro-ethyl)acetamide* (**2**). A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stir bar and fitted with a glass stopper and a condenser. The top of the condenser is fitted with a T-joint allowing argon to sweep the effluent gases (HCl and sulfur dioxide) from the reaction into the exit duct of a well ventilated fume hood. The flask is charged with compound **1** (8.98 g, 57 mmol), thionyl chloride (7.1 g, 60 mmol) (Note 6) and heptane (65 mL) (Note 2). The resulting suspension is stirred and heated to 85 °C in an oil bath under argon until a clear solution has formed. Stirring is continued for 15 min before the mixture is allowed to cool to ambient temperature, whereupon the product starts to crystallize. After standing for 30 min, the crystals are collected by filtration, rinsed with heptane (2 x 25 mL) and dried under vacuum (25 °C, 1 mmHg) for 1 h to provide product **2** (9.3 g, 93%) as colorless crystals, which were used without further purification in the next step (Note 7).

C. *S-(1-Acetylamino-2,2,2-trifluoroethyl) O-ethyl dithiocarbonate* (**3**). A 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stir bar, is charged with *N*-(1-chloro-2,2,2-trifluoro-ethyl)acetamide **2** (9.2 g, 52 mmol) and EtOH (100 mL) (Note 2). Potassium *O*-ethyl xanthate (9.2 g, 57 mmol) (Note 8) is added in portions over a period of 5 min. The resulting mixture is stirred at ambient temperature for 15 min (Note 9) before the reaction is quenched with water (100 mL). The solution is extracted with ether/hexanes solution (7:3, 3 x 150 mL), the combined organic layers are dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to provide a solid residue which is dried under vacuum (25 °C, 1 mmHg) for 1 h to give xanthate **3** (12.5 g, 91%) as a white solid (Note 10).

D. *3-Acetylamino-1-ethoxythiocarbonylsulfanyl-4,4,4-trifluorobutyl acetate* (**4**). A flame-dried, 100-mL, two-necked, round-bottomed flask is fitted with magnetic stir bar, a glass stopper and a condenser connected to the argon line. The flask is charged with xanthate **3** (12.4 g, 47.5 mmol), vinyl acetate (5.1 mL, 54.6 mmol) (Note 11) and 1,2-dichloroethane (50 mL) (Note 11) and the resulting solution is heated under reflux in an oil bath for 15 min under argon. Four equal portions of lauroyl peroxide (473 mg each, 1.9 g overall, 10 mol%) (Notes 11–13) are added in intervals of 1.5 h to the refluxing solution. After 7 h under reflux, the solution is allowed to reach ambient temperature before the solvent is evaporated under reduced pressure to give adduct **4** as a pale yellow oil (17.8 g), which was used in the next step without further purification (Note 14).

E. *N-(3,3-Dimethoxy-1-trifluoromethyl-propyl)-acetamide* (**5**). A flame-dried, 250-mL, two-necked, round-bottomed flask is fitted with a large magnetic stir bar, a glass stopper and a reflux condenser connected to the argon line. The flask is charged with the crude radical adduct **4** (17.8 g), MeOH (100 mL) and (±)-10-camphorsulfonic acid (12.5 mol%, 1.37 g, 5.9 mmol) (Note 15). The mixture is refluxed in an oil bath for 24 h before it is cooled to ambient temperature. The solvent is evaporated under reduced pressure. The residue is dissolved in ethyl acetate (80 mL) and the organic phase is washed successively with saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium chloride (20 mL). The organic solvent is dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting brown syrup (11.8 g) is purified by flash chromatography on silica gel (Notes 16, 17) using hexanes/ethyl acetate (2:3) as the eluent to give *N*-(3,3-dimethoxy-1-trifluoromethyl-propyl)-acetamide (**5**) as colorless crystals (4.43 g, 41%) (Note 18).

2. Notes

1. 2,2,2-Trifluoro-1-methoxyethanol was obtained from Avocado (trifluoroacetaldehyde methyl hemiacetal), tech. 90% and acetamide was obtained from Acros, 99%. The checkers used 2,2,2-trifluoro-1-methoxyethanol purchased from ABCR and acetamide purchased from Riedel de Haën.

2. 1,4-Dioxane was obtained from SDS Carlo Erba and used as received. All the solvents (petroleum ether, ethyl acetate, heptane, acetone, ethanol, methanol, *tert*-butyl methyl ether) were obtained from SDS Carlo Erba and used as received. The checkers used reagent-grade solvents purchased from Acros.

3. (E. Merck, Darmstadt, 230-240 mesh) was used. The progress of the reaction was monitored by TLC on silica gel using hexanes/ethyl acetate

(3:2) as eluent. The product has an R_f = 0.15 (stained with potassium permanganate solution [300 mL of water, 3 g of $KMnO_4$, 20 g of K_2CO_3, 0.25 mL of acetic acid]).

4. The submitters reported purification of the crude product by recrystallization: Dichloromethane (60 mL) is added to the crude product and the resulting mixture is vigorously stirred for 10 min. The resulting white precipitate is filtered, washed twice with 30 mL of dichloromethane and dried under vacuum (25 °C, 1 mmHg) for 1 h to give a crop of pure product. The corresponding filtrate is concentrated under reduced pressure, diluted in 80 mL of ethyl acetate and washed twice with 20 mL of a half-saturated aqueous sodium chloride solution. The organic solvent is then dried over anhydrous magnesium sulfate, filtered and evaporated to give a semi-solid residue. Dichloromethane (30 mL) is added and the mixture stirred vigorously for 10 min. The resulting white precipitate is filtered, washed twice with 10 mL of dichloromethane and dried under vacuum (25 °C, 1 mmHg) for 1 h to provide a second crop of pure product. The two crops are combined to give amide **1** (53% yield). The checkers obtained 41% of product using this purification method.

5. The product exhibited the following properties: mp 117–119 °C; ^{1}H NMR (MeOD, 400 MHz) δ: 2.01 (s, 3 H), 4.83 (s, 2 H), 5.71 (m, 1 H).

6. Thionyl chloride (99.5%) was obtained from Acros and used as received; the checkers used thionyl chloride (99%) purchased from Fluka.

7. The product exhibited the following properties: mp 85–87 °C (heptane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.15 (s, 3 H), 6.33 (qd, J = 5.3, 11.0 Hz, 1 H), 7.31 (br. m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.0, 60.7 (q, J = 38 Hz), 121.8 (q, J = 277 Hz), 170.4; IR (film): 3279, 3037, 1684, 1530, 1375, 1349, 1244, 1192, 1150, 1133, 857, 788, 690 cm^{-1}; HRMS (EI): Calcd for $C_4H_5NOF_3Cl$: 175.0011; Found: 175.0010.

8. Potassium *O*-ethyl xanthate (99%) was obtained from Aldrich (listed under ethylxanthic acid potassium salt) and recrystallized from hot ethanol before use. The checkers used the commercial product as received.

9. The progress of the reaction was monitored by TLC analysis on silica gel using hexanes/ethyl acetate (4:1) as eluent; the product had an R_f = 0.23 (stained with *p*-anisaldehyde solution [(950 mL of ethanol, 95%, 35 mL of concentrated sulfuric acid, 26 mL of *p*-anisaldehyde, 10.5 mL of acetic acid)].

10. The product exhibited the following properties: mp 84–86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (t, J = 7.0 Hz, 3 H), 2.11 (s, 3 H), 4.70 (q, J

= 7.0 Hz, 2 H), 6.61 (qd, $J = 7.6, 9.7$ Hz, 1 H), 7.43 (d, $J = 9.7$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.6, 22.8, 57.9 (q, $J = 38$ Hz), 71.4, 123.5 (q, $J = 279$ Hz), 170.9, 207.1; IR (film): 3278, 2990, 2933, 1667, 1514, 1370, 1334, 1289, 1246, 1210, 1186, 1127, 1115, 1102, 1049, 857, 819, 684 cm^{-1}. The product obtained following the procedure was pure enough for use in the next step. However, it could be recrystallized by dissolving 1 g of the compound in a hot mixture of 1 mL of ethyl acetate and 10 mL of heptane and allowing the solution to cool to room temperature whereupon the product crystallized (yield of crystallization > 85%). Anal. Calcd for $C_7H_{10}F_3NO_2S_2$: C, 32.18; H, 3.86. Found: C, 32.57; H, 3.91.

11. Vinyl acetate (99+%) and lauroyl peroxide (DLP, 97%) were obtained from Aldrich, and used as received. 1,2-Dichloroethane (99+%) was purchased from SDS Carlo Erba and used as received. The checkers used 1,2-dichloroethane (99%) purchased from KMF.

12. When performed on a smaller scale (4.28 g of xanthate **3**) complete conversion was reached with only 3 portions of lauroyl peroxide with a reaction time of only 4.5 h.

13. The progress of the reaction was followed by TLC analysis on silica gel using hexanes/ethyl acetate (4:1) as eluent and visualization was performed with *p*-anisaldehyde solution. The product had an $R_f = 0.075$.

14. The product exhibited the following properties: ^1H NMR ($CDCl_3$, 400 MHz, mixture of diastereomers) δ: 1.30 (br. t, 3 H), 1.41 (t, $J = 7.0$ Hz, 3 H), 2.02 (s, 6 H), 2.07 (s, 6 H), 2.10–2.27 (m, 2 H), 2.44–2.51 (m, 2 H), 4.61–4.67 (m, 4 H), 4.79–4.85 (m, 2 H), 6.54 (dd, $J = 3.0, 9.7$ Hz, 2 H), 6.65 (m, 2 H); IR (CCl_4): 3429, 2982, 1767, 1706, 1503, 1369, 1235, 1188, 1137, 1049 cm^{-1}. MS (ESI): 370 ($[M+Na]^+$).

15. (±)-10-Camphorsulfonic acid was purchased from Acros, 98%, and used as received.

16. Approximately 150 g of silica (E. Merck, Darmstadt, 230-240 mesh) was used with hexanes/ethyl acetate (2:3) as the eluent, $R_f = 0.16$ (stained with potassium permanganate solution).

17. The submitters reported that the crude product could be purified by crystallization by cooling a solution in Et_2O (20 mL) to −78 °C (52% yield). The checkers, however, experienced problems caused by gelation of the mixture and therefore utilized chromatographic purification.

18. The product exhibited the following properties: mp 61–63 °C (ether). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.83 (ddd, $J = 3.9, 9.8, 14.2$ Hz, 1 H), 2.03 (s, 3 H), 2.04 (ddd, $J = 3.3, 7.6, 14.2$ Hz, 1 H), 3.34 (s, 3 H), 3.36

(s, 3 H), 4.46 (dd, $J = 7.6, 3.9$ Hz, 1 H), 4.75 (m, 1 H), 6.89 (d, $J = 9.6$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.9, 31.7, 47.6 (q, $J = 32$ Hz), 53.1, 53.9, 101.6, 125.2 (q, $J = 280$ Hz), 170.6; IR (CCl_4): 3285, 3072, 2939, 2834, 1665, 1551, 1437, 1375, 1299, 1265, 1181, 1135, 1064 cm^{-1}. MS (EI) *m/z* (rel. intensity): 198 (45) 139 (58), 124 (56), 75 (100); HRMS (ESI): 252 ($[M+Na]^+$). Anal. Calcd for $C_8H_{14}F_3NO_3$: C, 41.92; H, 6.16. Found: C, 41.84; H, 6.09.

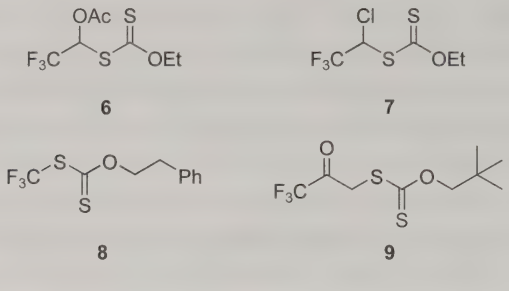
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The introduction of fluorine atoms in a given molecule often dramatically alters its chemical properties and its pharmacological profile in the case of a biologically active substance.[2] As a consequence, much ongoing effort has been devoted to the development of practical synthetic routes to the various classes of fluorinated compounds.[3] Radical reactions have proved quite useful in this respect. Xanthates, with their unique ability to mediate difficult radical processes such as intermolecular additions to non-activated olefins,[4] provide a collection of highly efficient reagents for the assembly of fluorinated derivatives. Some of these reagents are displayed in Figure 1. The transformation described above is representative of the use of xanthate **3**.[5] Vinyl acetate can be replaced by a number of other olefinic traps, as shown by the examples in the Table (entries 1-5).[5] Xanthates **6** and **7** can be prepared by a modification of the route devised for the synthesis of compound **3**.[6] They also add efficiently to various olefins as indicated by the examples in entries 6-10 in the Table.[6] A simple trifluoromethyl group can be introduced by the use of xanthate **8** (entry 11),[7] whereas reagent **9** gives directly a trifluoromethyl ketone (entry 12).[8]

Figure 1: Reagents for the assembly of fluorinated derivatives


6

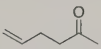
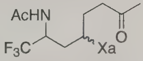
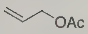
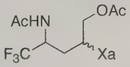
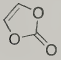
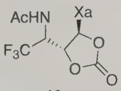
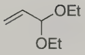
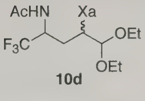
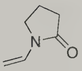
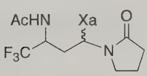
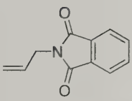
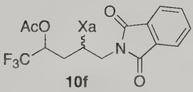
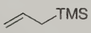
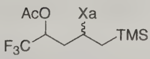
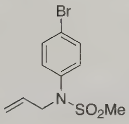
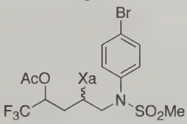
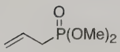
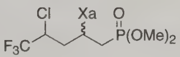
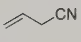
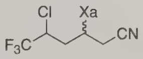
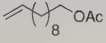
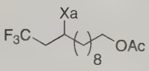
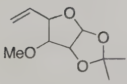
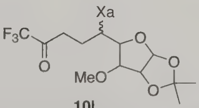
7

8

9

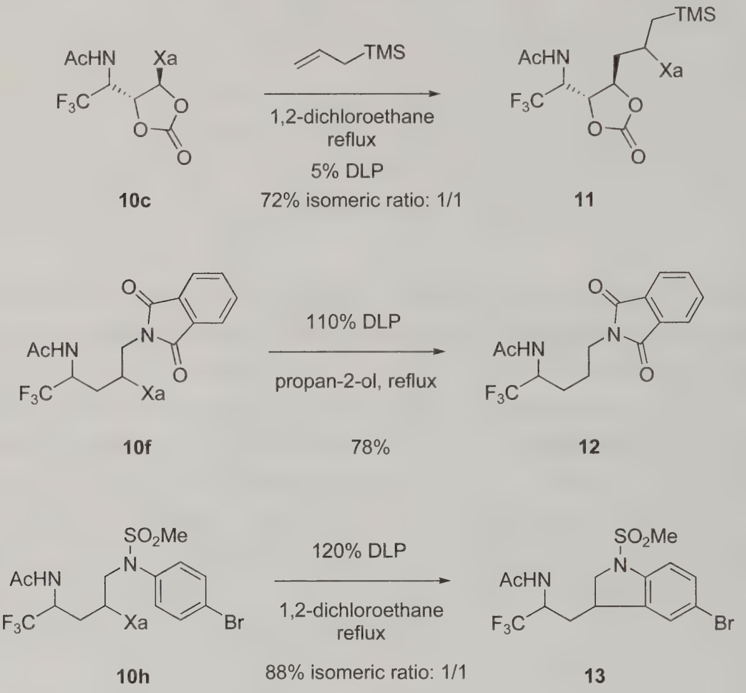
This approach to fluorinated derivatives combines efficiency with flexibility. The presence of the xanthate in the product can be exploited in many ways, since it provides an entry into the extremely rich chemistry of sulfur. It also allows the implementation of a second radical transformation, as shown by the three examples given in Scheme 1. The first example involves radical addition to allyl trimethylsilane leading to the densely functionalized structure **11**.[5] The second transformation illustrates a process for the tin-free reductive removal of the xanthate group (**10f** to **12**).[6] The last example (**13**) highlights the possibility of performing ring closures onto aromatic rings, providing a simple and direct entry into indolines.[6]

Table 1: Radical Additions of Xanthates (Xa = S-C(=S)OEt).

Entry	Xanthate	Olefin	Reaction time (h)	Adduct	Yield %	Isomeric ratio
1	3		1.5	 **10a**	88	1/1
2	3		1.5	 **10b**	84	1/1
3	3		6	 **10c**	72	1/1
4	3		1.5	 **10d**	95	6/43
5	3		3	 **10e**	62	6/4
6	6		4.5	 **10f**	78	1/1
7	6		1.5	 **10g**	80	2/3
8	6		8	 **10h**	82	1/1
9	7		3	 **10i**	27*	3/2
10	7		3	 **10j**	52	2/1
11	8		4.5	 **10k**	84	
12	9		3	 **10l**	80	2/3

* yield based on the starting trifluoroacetaldehyde hemiacetal.

Scheme 1: Radical transformations of adducts (DLP = dilauroyl peroxide)



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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

2,2,2-Trifluoro-1-methoxyethanol; (431-46-9)

Acetamide; (60-35-5)

N-(2,2,2-Trifluoro-1-hydroxyethyl)-acetamide; (6776-45-0)

Thionyl chloride; (7719-09-7)

N-1-(Chloro-2,2,2-trifluoroethyl)acetamide; (6776-46-1)

Potassium *O*-ethyl xanthate: Carbonodithioic acid, *O*-ethyl ester, potassium salt; (140-89-6)

S-(1-Acetylamino-2,2,2-trifluoroethyl) *O*-ethyl dithiocarbonate: Carbonodithioic acid, *S*-[1-(acetylamino)-2,2,2-trifluoroethyl] *O*-ethyl ester; (583029-16-7)

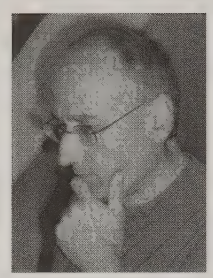
Lauroyl peroxide: Peroxide, bis(1-oxododecyl); (105-74-8)

Vinyl acetate: Acetic acid ethenyl ester (108-05-4)

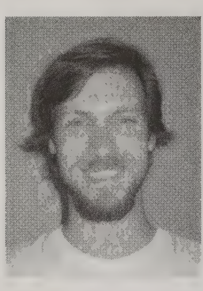
3-Acetylamino-1-ethoxythiocarbonylsulfanyl-4,4,4-trifluorobutyl acetate: Carbonodithioic acid, *S*-[3-(acetylamino)-1-(acetyloxy)-4,4,4-trifluorobutyl] *O*-ethyl ester: (583028-99-3)

(±)-10-Camphorsulfonic acid; (5872-08-2)

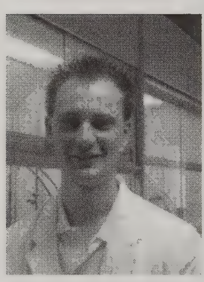
N-(3,3-Dimethoxy-1-trifluoromethyl-propyl)-acetamide: Acetamide, *N*-[3,3-dimethoxy-1-(trifluoromethyl)propyl]-; (583029-14-5)



Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research interests concern the study and development of new reactions and processes.

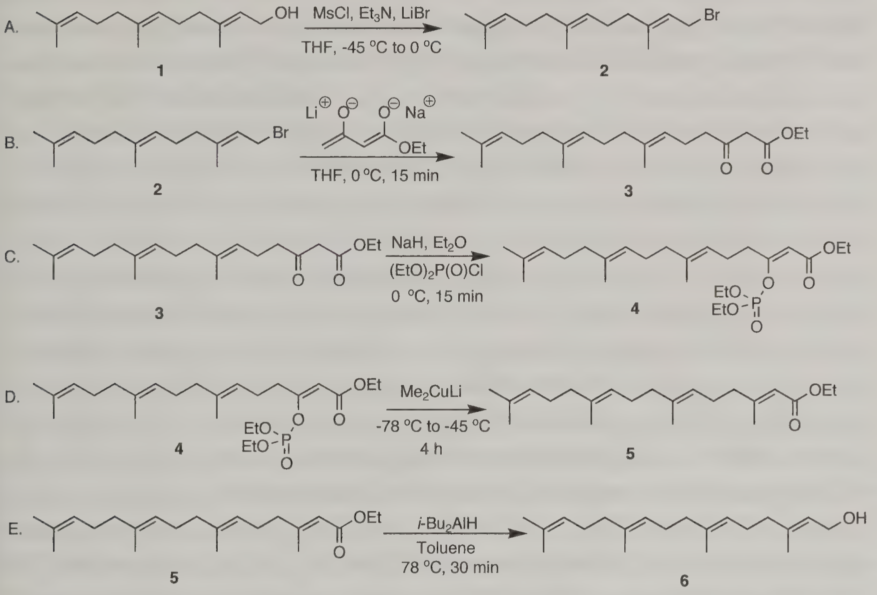


Fabien Gagosz graduated from the Chemistry Scool of Strasbourg in 1997. He obtained his PhD in 2002 from the Ecole Polytechnique in Palaiseau. He worked under the supervision of Prof. Samir Z. Zard on the development of new radical reactions with applications to the synthesis of alkaloids, phosphorylated and fluorinated compounds. He then joined Prof. W. B. Motherwell at the University college of London in 2003 as a postdoctoral associate. He returned to the Ecole Polytechnique in 2004 and joined the CNRS as Chargé de Recherches. His current independent research focuses on the development of new gold(I) catalysts and their use in the design of new synthetic methodologies.



Daniel Laurich was born in 1982 in Essen, Germany. After completing gymnasium (high school), he started his education in 1999 as a laboratory assistant at the Max-Planck-Institute for Coal Research in the group of Professor Alois Fürstner. He completed these studies in 2002 and remained in the group to work on various projects ranging from organometallic chemistry to natural product total synthesis. In 2003, he decided to further his experimental training by beginning studies to become a laboratory technician.

STEREOSELECTIVE ISOPRENOID CHAIN EXTENSION WITH ACETOACETATE DIANION: (*E*, *E*, *E*)-GERANYLGERANIOL FROM (*E*, *E*)-FARNESOL



Submitted by Yinghua Jin, Frank G. Roberts, and Robert M. Coates.[1]
Checked by Hillary M. Peltier and Jonathan A. Ellman.

1. Procedure

A. *(E, E)-Farnesyl bromide.* A flame-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, two rubber septa, and a nitrogen inlet connected to a mineral oil bubbler, is charged with 10.0 g (11.3 mL, 45.0 mmol) of (*E*, *E*)-farnesol (Note 1) and 150 mL of THF (Note 2). The solution is stirred and cooled in a dry ice/acetonitrile bath (temperature –45 °C to –47 °C), while methanesulfonyl chloride (6.70 g, 4.53 mL, 58.5 mmol) (Note 3) is added through one septum via syringe over 5 min. Triethylamine (9.10 g, 12.6 mL, 89.9 mmol) (Note 4) is then added through one septum by syringe over 5 min. A white solid precipitates during the addition, and the resulting suspension is stirred at –45 °C to –47 °C for 45 min. A room temperature solution of lithium bromide (15.6 g, 180

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mmol) (Note 5) in 50 mL of THF is prepared in a separate flask and added by cannula transfer over 5 min. The dry ice/acetonitrile bath is removed, and the suspension is allowed to warm to 0 °C with an ice-bath. The yellowish mixture is stirred at 0°C for 1 h. The reaction mixture is poured into 300 mL of ice water. The aqueous layer is separated and extracted with three 150-mL portions of cold diethyl ether (Note 6). The combined organic extracts are sequentially washed with ice-cold saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$ (Note 7), filtered, and concentrated by rotary evaporation and vacuum drying to give 11.6 g of (*E*, *E*)-farnesyl bromide as a light yellow oil which is used in the next step without purification (Note 8).

B. *(6E, 10E)-Ethyl 7,11,15-Trimethyl-3-oxohexa-deca-6,10,14-trienoate.* A flame-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, two rubber septa, and a nitrogen inlet connected to a mineral oil bubbler, is charged with a 60% dispersion of sodium hydride in mineral oil (5.32 g, 133 mmol) (Note 9). The mineral oil is removed by washing with three 10-mL portions of hexanes, allowing the sodium hydride to settle and withdrawing the supernatant solvent with a syringe. Tetrahydrofuran (100 mL) (Note 2) is added, and the hydride suspension is stirred and cooled in a 0 °C ice-bath as ethyl acetoacetate (15.8 g, 15.5 mL, 121 mmol) (Note 10) is added dropwise via syringe over 15 min. The light yellow solution of the sodium enolate is stirred at 0 °C for an additional 15 min (Note 11). A solution of *n*-BuLi in hexane (59.2 mL, 2.15 M, 127 mmol) (Note 12) is then added by syringe over 15 min. The resulting orange solution of acetoacetate dianion is stirred at 0 °C for 15 min. A room temperature solution of farnesyl bromide (11.6 g, 40.6 mmol) in 20 mL of THF is added by cannula transfer over 10 min. The resulting orange suspension is stirred at 0 °C for 15 min, aqueous HCl (1N, 300 mL) is added, and the aqueous layer is separated and extracted with diethyl ether (3 x 150 mL). The combined organic extracts are washed sequentially with saturated aqueous $NaHCO_3$ (2 x 200 mL) and brine (2 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation and vacuum drying to give 21.6 g of crude product. The excess ethyl acetoacetate is removed by Kugelrohr distillation (2 h, 60 °C, 0.4 mmHg) to afford 16.0 g of β-keto ester **3** as an orange oil. The residue is loaded onto a column of 220 g of silica gel (Note 13) and eluted with 300 mL of hexanes. At that point, collection of 50-mL fractions in glass tubes (25 x 150 mm) is begun, while elution is continued with 500 mL of 2% EtOAc-hexanes, 500 mL of 5% EtOAc-hexanes, 500 mL of 10% EtOAc-hexanes and then 500 mL of 15 % EtOAc-hexanes. The fractions are analyzed by TLC on silica gel with 30% EtOAc-hexanes as eluent and visualized with *p*-anisaldehyde staining reagent (Note 14). The product is obtained in fractions 20-33, which are combined and concentrated under reduced pressure using a rotary evaporator to yield β-keto ester **3** (11.8 g, overall 78% from farnesol) as a light yellow oil (Note 15).

C. (2Z,6E,10E)-Ethyl 7,11,15-Trimethyl-3-diethylphosphoryloxy-6,10,14-trienoate. A flame-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, two rubber septa, and a nitrogen inlet connected to a mineral oil bubbler, is charged with a 60% dispersion of sodium hydride in mineral oil (1.62 g, 40.6 mmol) (Note 9). The mineral oil is removed by washing with hexanes (3 x 10 mL) allowing the sodium hydride to settle and withdrawing the supernatant solvent with a syringe. Diethyl ether (150 mL) (Note 16) is added, and the mixture is stirred and cooled at 0 °C with an ice-bath. β-Keto ester **3** (11.7 g, 35.3 mmol) in 50 mL of diethyl ether is added slowly via cannula over 20 min, and the reaction mixture is stirred at rt for 20 min or until gas evolution ceases. The clear orange solution is then cooled to 0 °C, and neat diethyl chlorophosphate (9.13 g, 7.67 mL, 52.9 mmol) (Note 17) is added by syringe over 5 min. The mixture is stirred at 0 °C for 15 min, after which time the reaction is quenched by adding saturated aqueous NH_4Cl (300 mL). The aqueous layer is separated and extracted with diethyl ether (3 x 150 mL). The combined organic extracts are washed sequentially with saturated aqueous $NaHCO_3$ (2 x 200 mL) and brine (2 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporator and vacuum drying to give the crude enol phosphate **4** (16.9 g) as a yellow oil (Note 18).

D. *(2E,6E,10E)-Ethyl 3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenoate.* A flame-dried, 500-mL three-necked, round-bottomed flask, equipped with a magnetic stirring bar, one rubber septum, a thermometer, and a nitrogen inlet connected to a mineral oil bubbler, is charged with copper(I) iodide (12.1 g, 63.5 mmol) (Note 19) and 40 mL of diethyl ether (Note 16). The suspension is stirred and cooled at 0 °C in an ice bath as methyllithium in diethyl ether (98.8 mL, 1.29 M, 127 mmol) (Note 20) is added via syringe over 5 min. A yellow solid precipitates immediately during the addition, and the precipitate disappears after stirring at 0 °C for 30 min. The colorless or light tan solution is cooled to –78 °C using a dry ice/acetone bath and stirred magnetically, as a room temperature solution of enol phosphate **4** (16.9 g) in 50 mL of diethyl ether is added slowly over 20 min via cannula while maintaining the internal temperature below –60 °C (Note 21). The orange-red solution is stirred at –78 °C for 2 h. The reaction mixture is then allowed to warm to –45 °C using a dry ice/acetonitrile bath and stirred for 2 h, resulting in a dark purple mixture. Methyl iodide (4.50 mL, 10.3 g, 72.3 mmol) is added while stirring at –45 °C for 10 min (Note 22). The mixture is then poured into 300 mL of ice-cold 4:1 (v:v) saturated NH_4Cl and concentrated NH_4OH mixture, and stirred for approximately 1 h until all the copper salts disappear. The aqueous layer is separated and extracted with ether (3 x 150 mL). The combined organic extracts are washed sequentially with 10 % NH_4OH (2 x 200 mL), water (2 x 200 mL), and brine (2 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation and vacuum drying to give crude ester **5** (9.58 g) as a 19:1–20:1 mixture of trans and cis isomers according to GC analysis (Note 23).

E. *(E, E, E)-Geranylgeraniol.* A flame-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, two rubber septa, and a nitrogen inlet connected to a mineral oil bubbler, is charged with ester **5** (9.58 g, ~ 28.8 mmol) and toluene (100 mL) (Note 24). The solution is cooled in a dry ice/acetone bath (temperature –78 °C), and diisobutylaluminum hydride in hexanes (86.4 mL, 86.4 mmol) (Note 25) is added slowly via syringe through one of the septa over 20 min. After 30 min at –78 °C, the reaction is quenched by careful addition of methanol (10 mL) via a glass pipette over approximately 10 min (Note 26). The mixture is allowed to warm to room temperature and poured into a mixture of saturated NH_4Cl (250 mL) and 1N HCl (250 mL) with stirring, and the stirring is continued for 30 min. The aqueous layer is separated and extracted with ether (3 x 200 mL). The combined organic extracts are sequentially washed with water (2 x 200 mL) and brine (2 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporator and vacuum drying. The concentrated residue is loaded onto a column (5.0 x 21 cm) of 200 g of silica gel (Note 13) and eluted with 300 mL of hexanes. At that point, collection of 50-mL fractions in glass tubes (25 x 150 mm) is begun, while elution is continued with 500 mL of 5% EtOAc-hexanes, 500 mL of 10% EtOAc-hexanes, 500 mL of 15% EtOAc-hexanes, and then 500 mL of 20 % EtOAc-hexanes. The fractions are analyzed by TLC on silica gel with 30% EtOAc-hexanes as eluent and visualized with *p*-anisaldehyde staining reagent (Note 14). The product is obtained in fractions 24-42, which are combined and concentrated under reduced pressure using a rotary evaporator to yield geranylgeraniol (7.20 g, overall 70% from β-keto ester **3**) (Note 27).

2. Notes

1. *Trans*, *trans*-farnesol (~95%) was purchased from the Fluka Chemical Corp. and was used without further purification.

2. Tetrahydrofuran was purchased from Fisher Scientific Co. and passed through an alumina column (checkers) or purchased from Burdick and Jackson and freshly distilled from sodium/benzophenone under nitrogen (submitters).

3. Methanesulfonyl chloride (>99.5 % purity) was purchased from Aldrich Chemical Co. and used as received. When this reagent was taken from a previously opened container, it was distilled from P_2O_5 before use.

4. Triethylamine (reagent grade) was purchased from Fisher Scientific Co., distilled from calcium hydride, and stored over potassium hydroxide pellets.

5. Lithium bromide was purchased from Fisher Scientific Co. and flame-dried under vacuum before use.

6. Unless otherwise indicated, the solvents used were of reagent grade quality and were used without further purification.

7. Anhydrous $MgSO_4$ was purchased from Fisher Scientific Co.

8. Bromide **2** is prone to decomposition and should be kept cold by adding ice during the extractions and washings. It should be stored in a freezer (approximately –20 °C) no longer than one day. The physical data for (*E*, *E*)-farnesyl bromide (provided by submitters) follow: TLC $R_f = 0.72$ (7:3 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (br s, 6 H, 2CH_3), 1.69 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 1.97–2.13 (m, 8 H, 4CH_2), 4.03 (d, $J = 8.3$ Hz, 2 H, CH_2Br), 5.08–5.11 (m, 2 H, vinyl *H*), 5.54 (br t, $J = 8.3$ Hz, 1 H, vinyl *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 16.3, 17.9, 25.9, 26.3, 26.9, 30.0, 39.7, 39.9, 120.7, 123.6, 124.5, 131.6, 135.8, 143.8.

9. Sodium hydride was purchased from Acros Organics and used as received.

10 Ethyl acetoacetate was purchased from Aldrich Chemical Co. and purified by washing with saturated aqueous $NaHCO_3$ and water, drying over $MgSO_4$, and distilling under reduced pressure (bp 30–32 °C, 1 mmHg).

A slower, incomplete reaction (89 % conversion after 5 h at 0 °C, 68% yield based on conversion) occurred when only 1.2 equiv of ethyl acetoacetate was used, instead of 3.0 equiv, under otherwise identical conditions.

11. ***Caution:*** Vigorous evolution of hydrogen occurs. The mixture should be stirred until gas evolution ceases.

12. *n*-Butyllithium in hexanes was purchased from Aldrich Chemical Co. and titrated using 2,6-di-*tert*-butyl-4-methylphenol and 1,10-phenanthroline (checkers).

13. Silica gel 60 230-400 mesh ASTM was purchased from Merck and Co. The 6.2-cm diameter glass column was packed with silica gel (6.2 x 14.5 cm) and hexanes.

14. Anisaldehyde staining reagent was prepared by adding, in small portions with stirring, 6.5 mL of concentrated H_2SO_4, 2.5 mL of glacial acetic acid, and 5 mL of *p*-anisaldehyde in the order listed to 186 mL of cold 95% EtOH.

15. The absolute yield of β-keto ester **3** was determined in one of the submitters' runs prior to chromatography (17.3 g of crude **3**) by ^{1}H NMR analysis using mesitylene as a standard. A solution of crude product (47 mg) and mesitylene (11 mg) in chloroform-*d* was prepared. Integrations of the ^{1}H NMR spectrum showed a 1.00:0.79 molar ratio of the product and the standard, indicating the yield was 13.7 g (91 %). The submitters obtained 11.7–12.2 g of β-keto ester **3** (overall 78–81% from farnesol) after chromatography as mixtures of keto and enol tautomeric forms. The physical data (supplied by the checkers) for pure β-keto ester **3** (6.7:1 mixture of keto and enol tautomeric forms) are as follows: TLC: $R_f = 0.60$ (7:3, hexanes/ethyl acetate); IR: 1721, 1745, 2920 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (t, $J = 7.2$ Hz, 3 H, CH_3), 1.59 (br s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.68 (br s, 3 H, CH_3), 2.00–2.13 (m, 8 H, 4 CH_2), 2.28 (q, $J = 7.5$ Hz, 2 H, CH_2), 2.56 (t, $J = 7.5$, 2 H, CH_2), 3.42 (s, 2 H, CH_2), 4.19 (q, $J = 7.2$ Hz, 2 H, CH_2), 4.97 (s, 0.164 H, -C(OH)=C*H*-), 5.06–5.09 (m, 3 H, vinyl *H*), 12.1 (s, 0.146 H, -C(O*H*)=CH-).; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.4, 16.33, 16.35, 18.0, 22.5, 26.0, 26.9, 27.1, 39.9, 40.0, 43.4, 49.7, 61.7, 122.4, 124.4, 124.7, 131.6, 135.4, 137.1, 167.6, 202.9. Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.63; H, 10.47.

16. Diethyl ether was purchased from Fisher Scientific Co. and passed through an alumina column (checkers) or freshly distilled from sodium/benzophenone under nitrogen (submitters).

17. Diethyl chlorophosphate (97%) was purchased from Aldrich Chemical Co. and was used as received.

18. The submitters recommend using the unpurified enol phosphate since an attempt to purify the intermediate by large-scale flash column chromatography resulted in reduced yield, probably owing to the decomposition of the product. The crude enol phosphate **4** (18.7 g) was analyzed by the submitters by ^{1}H NMR spectroscopy using mesitylene as a standard. A solution of 20 mg of enol phosphate **4** and 10 mg of mesitylene in chloroform-*d* was prepared. Integrations of the ^{1}H NMR spectrum showed a 1.00:2.08 molar ratio of the product and the standard, indicating the purity of the crude product was 90 %. A 70-mg sample of enol phosphate was purified by the submitters with flash column chromatography using 30 % ethyl acetate in hexanes as eluent to yield 27 mg of pure enol phosphate **4**: TLC: $R_f = 0.26$ (7:3 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, $J = 7.1$ Hz, 3 H, CH_3), 1.36 (td, $J = 7.1$, 1.2 Hz, 6 H, $2CH_3$), 1.59 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.95–2.07 (m, 8 H, $4CH_2$), 2.27 (q, $J = 7.3$ Hz, 2 H, CH_2), 2.45 (t, $J = 7.6$ Hz, 2 H, CH_2), 4.15 (q, $J = 7.2$ Hz, 2 H, CH_2), 4.26 (dq, $J = 7.8$, 7.1 Hz, 4 H, $2CH_2$), 5.07–5.11 (m, 3 H, vinyl *H*), 5.35 (s, 1 H, vinyl *H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.4, 16.16, 16.23, 16.28, 16.29, 17.9, 25.1, 25.9, 26.8, 26.9, 35.4, 39.9 (d, $J = 7.6$ Hz), 60.1, 64.9 (d, $J = 6.1$ Hz), 105.5 (d, $J = 7.4$ Hz), 122.0, 124.2, 124.5, 131.5, 135.3, 137.0, 161.6 (d, $J = 7.3$ Hz), 164.0; ^{31}P NMR ($CDCl_3$, 202 MHz) δ –7.6.

19. Copper(I) iodide (98%) purchased from Aldrich Chemical Co. was used as received.

20. Methyllithium in diethyl ether was purchased from Aldrich Chemical Co. and titrated using 2,6-di-*tert*-butyl-4-methylphenol and 1,10-phenanthroline (checkers).

21. Enol phosphate **4** should be added slowly. The coupling reaction was exothermic; fast addition of enol phosphate **4** caused a temperature rise that led to a lower *trans*/*cis* ratio.

22. Direct hydrolysis of the crude product with a mixture of ice-cold 5:1 (*v*/*v*) saturated NH_4Cl and concentrated NH_4OH afforded all *trans* ester **5** contaminated by approximately 5% of the simple reduction byproduct, (2*E*,6*E*,10*E*) ethyl 7,11,15-trimethylhexadeca-2,6,10,14-tetraenoate, which was inseparable by chromatography. Prior addition of methyl iodide decreased the amount of the reduction byproduct to ≤ 1%.

23. The unpurified ester **5** (11.1 g) was analyzed by the submitters in one run by ^{1}H NMR spectroscopy using mesitylene as internal standard. Integrations of the spectrum of the ester (26 mg) and mesitylene (10 mg) in chloroform-*d* showed a 1.00:1.17 molar ratio of the product and standard, indicating a purity of 90 %. In a different run a small sample (approximately 30 mg) of the crude product was purified by the submitters with flash column chromatography using 10 % ethyl acetate in hexanes as eluent to afford a characterization sample of pure ester **5**: TLC R_f = 0.72 (7:3 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.60–1.61 (m, 9 H, $3CH_3$), 1.69 (d, J = 1.1 Hz, 3 H, CH_3), 1.96–2.17 (m, 12 H, $6CH_2$), 2.17 (d, J = 1.1 Hz, 3 H, CH_3), 4.15 (q, J = 7.2 Hz, 2 H, CH_2), 5.08–5.13 (m, 3 H, vinyl *H*), 5.67 (m, 1 H, vinyl *H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 16.22, 16.25, 17.9, 19.0, 25.9, 26.2, 26.8, 27.0, 39.88, 39.92, 41.2, 59.7, 115.8, 123.1, 124.3, 124.6, 131.5, 135.3, 136.4, 160.1, 167.1.

24. Toluene was purchased from Fisher Scientific Co. and passed through a column of alumina (checkers) or dried over 4Å molecular sieves (submitters).

25. Diisobutylaluminum hydride (1.0 M in hexanes) was purchased from Aldrich Chemical Co.

26. ***Caution:*** Methanol should be added very slowly to avoid vigorous gas evolution.

27. The submitters obtained 6.90–7.94 g of geranylgeraniol (68–77% yield from β-keto ester **3**). Physical data for geranylgeraniol (**6**) (supplied by the checkers): TLC: R_f = 0.43 (7:3 hexanes/ethyl acetate); IR: 1445, 1668, 2921, 3319 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (br s, 9 H, $3CH_3$), 1.67 (br s, 6 H, $2CH_3$), 1.98–2.13 (m, 12 H, $6CH_2$), 4.13 (d, 2 H, J = 7.0), 5.07–5.10 (m, 3 H, vinyl *H*), 5.40 (t, J = 7.0 Hz, 1 H, vinyl *H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2, 16.3, 16.6, 18.0, 26.0, 26.6, 26.9, 27.0, 39.9, 39.99, 40.0, 59.6, 123.7, 124.1, 124.5, 124.7, 131.5, 135.2, 135.6, 139.9. Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.58; H, 12.16. The purity of geranylgeraniol (**6**) was determined to be 96 % according to GC analysis. GC analysis was performed on a Shimadzu GC-14A with 30-m Restek Rtx-5 column, and the sample was analyzed using the following parameters, initial temperature 40 °C, hold for 5 min, 20 °C/min until 300 °C, hold for 5 min.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(*E, E, E*)-Geranylgeranyl diphosphate (GGPP) is considered to be the universal substrate for diterpene cyclases, prephytoene synthase, and many prenyl diphosphate synthases,[2] as well as cosubstrate for protein geranylgeranyl transferases I and II.[3] The diphosphate ester is readily prepared from (*E, E, E*)-geranylgeraniol (**6**, GGOH) by conversion to the corresponding allylic chloride, bromide, or diethyl phosphate followed by S_N2 displacement with tetrabutylammonium pyrophosphate.[4,5] Although both GGOH and GGPP are commercially available, the prices are quite high, and there is need for reliable methods to access different labeled forms and analogues as pure all trans isomers for research on diterpene synthases and transferases. The present five-step procedure (**1** → **6**) effects isoprene chain extension of (*E, E*)-farnesol to give 6.9–7.9 g of the isoprenylogue **6** in 53–61% overall yield and with high E selectivity using Weiler's acetoacetate dianion alkylation-enol phosphate coupling methods.[6,7] 6-FluoroGGOH was prepared in the same way from 2-fluorofarnesol.[8] A similar route to **6** utilizes a Suzuki reaction of the enol triflate related to enol phosphate **4** to obtain α,β-enoate **5**.[9]

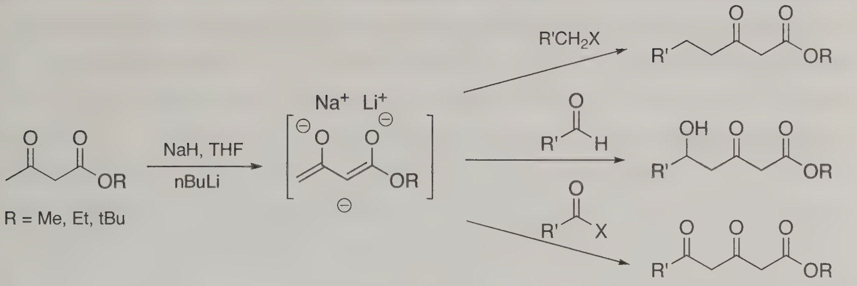
The most common syntheses of (*E, E, E*)-geranylgeraniol (**6**) in the literature proceed by C_2 chain extensions of (*E, E*)-farnesylacetone, reactions that invariably afford mixtures of 2E and 2Z isomers of esters or alcohols. Farnesylacetone has been synthesized from farnesol derivatives by traditional α-alkylation of acetoacetate[10a,b] and by alkylation of lithiated acetone *N,N*-dimethylhydrazone,[10c] and by Wittig olefination of the keto aldehyde generated from ozonolysis of isoprene cyclic trimer.[11] Conversion to isomeric mixtures of geranylgeranoates or geranylgeraniol has been accomplished by an acetylide addition-reduction-allylic rearrangement sequence,[10a] by Horner-Wadsworth-Emmons olefinations,[12] by ethoxyacetylene addition and hydrolysis,[10b,13] and by vinylmetal addition followed by allylic rearrangement.[10c,11] Reductions of ester **5** to the GGOH have been carried out with $LiAlH_4$, $i Bu_2AlH$, and $LiAlH_4$-$AlCl_3$.

Geranylgeraniol has also been obtained by Peterson and Wittig olefinations to complete the isoprene units at the opposite ends of the chain.[14] A convergent approach involves allylic couplings of two C_{10} geraniol derivatives,[15] geranylbarium alkylation,[16a] and an allyl silane-acetal S_E' method.[16b] Palladium-mediated couplings of an α-sulfonylfarnesyl-1-carboxylate with isoprene 3,4-epoxide and of methyl farnesoate with α-sulfonyl-γ,γ-dimethylallylcarboxylate have been reported.[17] Synthesis of the 2E, 6Z, 10E isomer has been achieved by sequential Pd-catalyzed couplings of zincates with vinyl iodides followed by zirconocene-mediated addition of Me_3Al to a trienyne intermediate to form the hydroxyl-bearing isoprene unit.[18] A patent describes the separation of geranylgeranyl stearate isomers by crystallization at low temperature.[19]

Although numerous methods for isoprenoid chain extensions have been investigated,[20] the present approach[6a,b,7] has the important advantages of high E-selectivity at both the 2,3 and 6,7 double bonds, satisfactory overall yield, and the potential to form 2Z,6E, 2E,6Z, and 2Z,6Z isomers.[21] The 5-step sequence begins with conversion of (*E*,*E*)-farnesol (**1**) to the corresponding bromide (**2**) with methanesulfonyl chloride, triethylamine, and lithium bromide in THF at –45 to 0 °C.[22] The Li/Na dianion is generated by lithiation of sodio acetoacetate with *n*-butyllithium in THF at 0 °C, and subsequent γ-alkylation with the unpurified bromide affords β-keto ester **3**. Phosphorylation of the sodium enolate with diethyl chlorophosphate in ether gives rise to all trans enol phosphate **4** which undergoes vinylic coupling with lithiodimethyl cuprate in ether solution at –78 to –45 °C to give (*E*,*E*,*E*)-ethyl geranylgeranoate (**5**) in good yield and ~20:1 E-selectivity. Reduction of the ester with isobutylaluminum hydride in toluene provides (*E,E*,*E*)-geranylgeraniol (**6**) in 53-61% overall yield after purification by chromatography on silica gel.

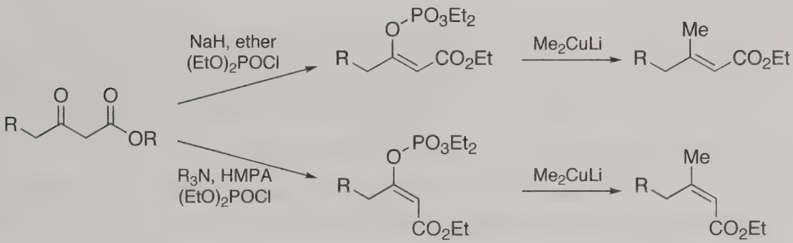
Acetoacetate dianion is a very useful carbon nucleophile for C-C bond formation at the γ-position and for accessing a wide variety of β-keto esters.[23] It is sufficiently stable to undergo alkylations with unactivated primary halides and epoxides,[24] and aziridines bearing *N*-sulfonyl or *N*-phosphoryl groups.[25] Reactions with carbonyl electrophiles afford δ-hydroxy-β-keto esters and δ, β-diketo esters (Scheme 1).[26]

Scheme 1



Coupling of enol phosphates with organocopper reagents offers a versatile, stereoselective synthesis of tri- and tetra-substituted α,β-unsaturated esters from β-keto esters with either double bond configuration. *O*-Phosphorylation of chelated sodium enolates of β-keto esters with diethyl or diphenyl phosphoryl chlorides in diethyl ether give rise to the Z (trans) enol phosphate isomers[6a] whereas the E (cis) isomers can be obtained through reactions with tertiary amine bases in polar solvents, eg Et_3N or $i$$Pr_2NEt$ in HMPA (Scheme 2).[21,27] Vinylic couplings with methyl, primary alkyl, and *t*-butyl cuprates or Grignard reagents in the presence of Cu(I) salts usually take place efficiently with retention of the double bond geometry. Palladium-catalyzed Suzuki reactions of Z and E enol triflates with methyl-, *t*-butyl-, cyclopropyl-, and phenylboronic acids have been employed in similar syntheses of E and Z isoprenoid esters and their C-3 analogues.[9]

Scheme 2



(*E,E,E*)-Geranylgeraniol (**6**) has other research applications beyond its conversion to the diphosphate. The forms labeled with deuterium and tritium at C-1 [1,1-$^2H_2$]- and [1-^{3}H]**6** can be oxidized to the corresponding labeled aldehydes which are reduced to (*R*)- and (*S*)-[1-$^2H_1$]- and [1-^{3}H]**6** for studies on stereochemistry of diterpene cyclase and transferase reactions.[5,28] The terminal double bonds of the benzyl ether and acetate derivatives of **6** are converted to the 14,15 bromohydrins by hypobromination reactions with *N*-bromosuccinimide in aqueous THF or DME.[5,10b,29] The bromohydrins are readily cyclized to the epoxides and then converted to 14,15-oxidogeranylgeraniol.[10b] Acid-catalyzed hydrolysis to the 14,15-diol and oxidative cleavage with periodate affords the trisnoraldehyde that is a key intermediate in synthesis of **6** bearing deuterium in the terminal methyl positions by E- or Z-selective olefinations and deuteride reductions.[28a] Reductive amination of the trisnoraldehyde acetate and hydrolysis gives 14-aza-14,15-dihydro **6**,[5] the diphosphate of which is a potent inhibitor abietadiene synthase.[30]

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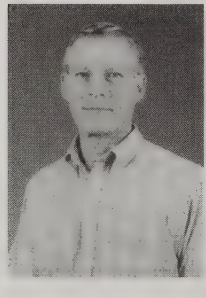
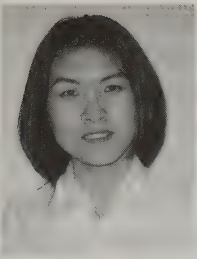
Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*E*, *E*)-Farnesol; (106-28-5)
Methanesulfonyl chloride; (124-63-0)
Ethyl acetoacetate: Butanoic acid, 3-oxo-, ethyl ester; (141-97-9)
Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester; (814-49-3)
Diisobutylaluminum hydride: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)



Robert M. Coates was born in Evanston, Illinois, in 1938. He received his BS degree in chemistry from Yale University in 1960 and his Ph.D degree from the University of California-Berkeley with W. G. Dauben in 1964. After postdoctoral research at Stanford University with E. E. van Tamelen in 1964-1965, he joined the faculty in the Chemistry Department at the University of Illinois at Urbana-Champaign in 1965. His research has been primarily concerned with terpenes and carbocyclic compounds, stereochemistry and mechanism of isoprenoid biosynthesis, and design and synthesis of inhibitors and active site probes for terpene synthases.

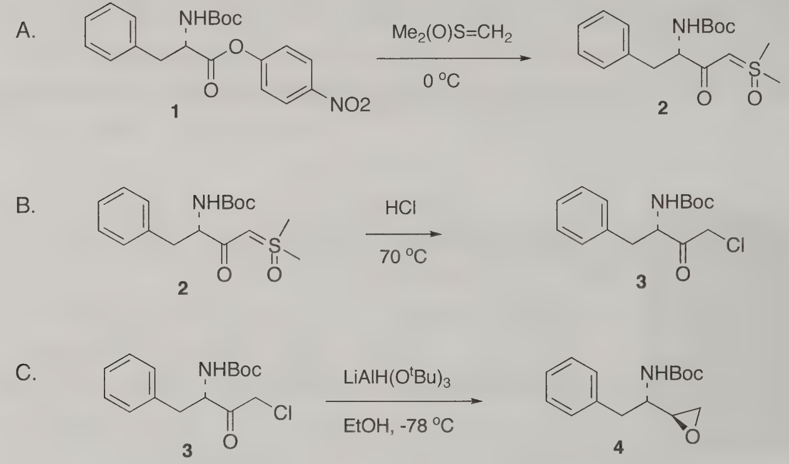


Yinghua Jin was born in Longjing, China in 1976. She received her BS degree in chemistry from Peking University in 2000. After graduation, she spent one year at University of Utah, working as a graduate assistant in the research group of Professor Frederick G. West. In 2001, she transferred to University of Illinois at Urbana-Champaign, where she completed her Ph.D degree in chemistry with Professor Robert M. Coates in 2006. Her graduate research was focused on mechanistic investigations of taxadiene biosynthesis by means of fluoro analogues of geranylgeranyl diphosphate and azanorcembrene enantiomers.

Frank G. Roberts was born in Chicago, Illinois, in 1982. He received his B.S. degree in chemistry from the University of Illinois at Urbana-Champaign in 2006 where he carried out undergraduate research on beyerane and kaurane diterpenes in R. M. Coates' laboratory. In the summer 2005 he was an exchange student at the Ludwig Maximillian University, Munich, Germany, where he worked in Prof. Hendrik Zipse's group. He is currently a Freud Fellow at the University of Chicago pursing a Ph.D degree under the direction of Professor Milan Mrksich.

Hillary M. Peltier grew up in Jeannette, Pennsylvania. She earned a B.S. from the University of Michigan, Ann Arbor in 2002. That year, she began her doctoral studies at the University of California, Berkeley in the laboratories of Prof. Jonathan A. Ellman. Her graduate work has focused on the development of methods for the asymmetric synthesis of amines using *N-tert*-butanesulfinamde and the application of these methods toward the synthesis of biologically relevant molecules

SYNTHESIS OF AN *ANTI*-α-AMINO EPOXIDE BY ONE-CARBON HOMOLOGATION OF AN α-AMINO ESTER: (2*S*,3*S*)-1,2-EPOXY-3-(BOC-AMINO)-4-PHENYLBUTANE



Submitted by Dengjin Wang and William A. Nugent.[1]
Checked by Jason J. Kowal and David J. Mathre.

1. Procedure

A. *Dimethylsulfoxonium (S)-2-oxo-3-(Boc-amino)-4-phenylbutylide* (**2**). A 500-mL three-necked, round-bottomed flask is equipped with a large stir bar, a nitrogen inlet, a reflux condenser capped with a nitrogen outlet, and a rubber septum through which is inserted a temperature probe. The flask is flushed with nitrogen for 5 min and is then charged with trimethylsulfoxonium iodide (33.0 g, 150 mmol) (Note 1), which is added through a neck that is temporarily opened, and 150 mL of anhydrous tetrahydrofuran (Note 2), which is added by syringe through a septum. A 1.0 M solution of potassium *tert*-butoxide in tetrahydrofuran (150 mL, 150 mmol) (Note 3) is added via syringe through a septum, after which the mixture is heated at reflux for 2 h (Note 4). The resulting solution of dimethylsulfoxonium methylide (containing precipitated potassium iodide) is cooled to 0 °C. The reflux condenser is replaced with a 125-mL pressure-

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equalizing addition funnel containing a solution of Boc-L-phenylalanine 4-nitrophenyl ester (**1**) (19.3 g, 50.0 mmol) (Note 5) in 100 mL of anhydrous tetrahydrofuran and capped with a nitrogen outlet. The solution is added dropwise over 20 min so that the internal temperature does not exceed 5 °C. The mixture is stirred for 1 h at 0 °C. The flask is briefly opened by temporary removal of the addition funnel to allow addition of 50 mL of water and stirring is continued for 15 min at 0 °C. After warming to room temperature, the mixture is filtered through a short pad (3 mm) of Celite on a 100-mL fritted-glass Büchner funnel and the solvent is removed by rotary evaporation (25 °C, 20 mmHg). The concentrated mixture is rinsed into a 1-L separatory funnel with 200 mL of water and extracted with one 200-mL portion and two 100-mL portions of ethyl acetate (Note 6). The combined extracts are washed with one 50-mL portion of water and two 50-mL portions of brine. (In some cases solid product separates during the first extraction, but it redissolves when the organic phases are combined.) The solution is dried over sodium sulfate, filtered and concentrated by rotary evaporation (25 °C, 20 mmHg) to afford **2** as a light yellow solid (15.3–15.4 g, 90–91%) (Note 7), which is carried on to the next step without further purification.

B. *(S)-1-Chloro-3-(Boc-amino)-4-phenyl-2-butanone* (**3**). A 500-mL three-necked, round-bottomed flask is equipped with a stir bar, a nitrogen inlet, a reflux condenser capped with a nitrogen outlet, and a rubber septum through which is inserted a temperature probe. The flask is flushed with nitrogen for 5 min and is then charged with dimethylsulfoxonium (*S*)-2-oxo-3-(Boc-amino)-4-phenylbutylide (**2**) (13.6 g, 40 mmol), which is added through temporary removal of the reflux condenser. Anhydrous tetrahydrofuran (250 mL) is added by syringe through a septum. A 4.0 M solution of hydrogen chloride in 1,4-dioxane, (11.6 mL, 46.0 mmol) (Note 8) is added via syringe through the septum over 5 min at room temperature during which time a solid sulfoxonium salt separates. The mixture is then heated with stirring at reflux (70 °C) for 4 h. The reaction mixture stirs as a very thick slurry for the first 30 min of this period. After cooling to room temperature, the resulting homogeneous solution is transferred to a 1-L separatory funnel, to which is added 100 mL of ethyl acetate and 200 mL of hexanes (Note 9). The mixture is washed with two 200-mL portions of water, one 100-mL portion of saturated sodium bicarbonate solution, four 200-mL portions of water and one 100-mL portion of brine. (Note 10) The solution is dried over sodium sulfate and filtered through a 100-mL fritted-glass Büchner funnel. The filtrate is concentrated by rotary evaporation (25 °C, 20 mmHg) to obtain 13–14 g of a light yellow solid. This material is dissolved in 40 mL of hot hexanes (70 °C). Upon cooling, a solid separates which is collected by filtration on a 100-mL fritted-glass Büchner funnel and dried overnight at 25 °C and 0.5 mmHg to afford **3** (9.61–9.71 g, 81% yield) (Note 11) as an off-white solid.

C. *(2S,3S)-1,2-Epoxy-3-(Boc-amino)-4-phenylbutane* (**4**). A 500-mL three-necked, round-bottomed flask is equipped with a large stir bar (Note 12), a nitrogen inlet, a 125-mL pressure-equalizing addition funnel capped with a nitrogen outlet, and a rubber septum through which is inserted a temperature probe. The flask is flushed with nitrogen for 5 min and is then charged with (*S*)-1-chloro-3-(Boc-amino)-4-phenyl-2-butanone (**3**) (7.5 g, 25 mmol), which is added through temporary removal of the addition funnel. Anhydrous ethanol (200 mL, Note 13) is added by syringe through a septum. The addition funnel is opened slightly to allow delivery via syringe of a 1.0 M solution of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran (52.5 mL, 52.5 mmol) (Note 14). The flask is cooled to –78 °C (internal temperature) in a dry ice-acetone bath. The contents of the addition funnel are then added dropwise over 20 minutes so that the internal temperature does not exceed –70 °C. The mixture is stirred at this temperature for 2 h. The cooling bath is removed and the internal temperature is allowed to rise to –20 °C. The reaction is quenched through the addition of 50 mL of Rochelle's salt solution in one portion (Note 15). The bath is removed and stirring is continued for 15 min. The reaction mixture is concentrated by rotary evaporation (25 °C, 20 mmHg) to provide two liquid phases of ~80 mL combined volume. The concentrated mixture is transferred to a 1-L separatory funnel. An additional 200 mL of Rochelle's salt solution is added and the mixture is extracted with one 500-mL portion and one 150-mL portion of ethyl acetate. The combined extracts are washed with two 200-mL portions of water and one 200-mL portion of brine. The solution is dried over sodium sulfate, filtered and concentrated by rotary evaporation (25 °C, 20 mmHg) to obtain the crude product as a light yellow solid. This material is dissolved with heating in a mixture of 30 mL of ethyl acetate and 10 mL of hexanes (70 °C). Upon cooling, a solid separates which is collected by filtration on a 100-mL fritted-glass Büchner funnel and dried overnight at 25 °C and 0.5 mmHg to afford **4** (5.44–5.56 g, 82–84% yield) (Note 16) as a white solid.

2. Notes

1. Trimethylsulfoxonium iodide was purchased from the Aldrich Chemical Company, Inc. and used as received.

2. Anhydrous tetrahydrofuran (<50 ppm water) was purchased from EM Science and used as received.

3. Potassium *tert*-butoxide (1.0 M in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc. and used as received.

4. This heating step was essential when the starting ester was potentially epimerizable. If this step was omitted in the case of sulfur ylide **2**, good chemical yields were obtained but the product was nearly racemic.

5. Boc-L-Phenylalanine 4-nitrophenyl ester was purchased from Bachem Bioscience, Inc. and used as received.

6. Ethyl acetate was purchased from EMD Chemicals, Inc. and was used as received.

7. An analytical sample of compound **2** that was dried for 24 h at room temperature at 0.5 mmHg had the following properties: mp (DSC) 163 °C. $[\alpha]_D^{25}$ –31.8 (c = 1.00, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (s, 9 H), 2.98 (m, 2 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 4.28 (m, 2 H), 5.22 (d, *J* = 8.8, 1 H), 7.15–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.3, 39.7, 41.7, 42.0, 57.8, 69.4, 79.2, 126.4, 128.1, 129.5, 137.6, 155.1, 186.5. Anal. Calcd for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13; S, 9.44 Found: C, 60.21; H, 7.61; N, 4.06. TLC: dichloromethane/methanol (95:5) $R_f = 0.35$.

8. Hydrogen chloride (4.0 M in dioxane) was purchased from Aldrich Chemical Company, Inc. and was used as received.

9. Hexanes was purchased from EMD Chemicals, Inc. and was used as received.

10. The multiple washes were required to completely remove an impurity (presumably co-product DMSO) that interfered with the crystallization of **3**.

11. The enantiomeric excess was determined to be >99% by supercritical fluid chromatography (Chiralcel OD-H, 250 x 4.6 mm, 5 μm particle size, 3% methanol in CO_2 mobile phase, 40 °C, 2 mL/min, 150 bar). Retention times for the (*R*)- and (*S*)-enantiomers were 6.2 and 6.8 min, respectively. Properties of **3** are as follows: mp (DSC) 103 °C. $[\alpha]_D^{25}$ = –43.3 (c = 1.00, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 9 H), 2.94–3.12 (m, 2 H), 4.00 (d, *J* = 16.2, 1 H), 4.18 (d, *J* = 16.2, 1 H), 4.68 (m, 1 H), 5.10 (b, 1 H), 7.14–7.47 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ:

28.3, 37.8, 47.5, 58.5, 80.6, 126.2, 129.0, 129.2, 135.7, 155.3, 201.5. Anal. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.15; H, 6.81; N, 4.72. TLC: hexanes/ethyl acetate (2:1) $R_f = 0.7$.

12. The checkers used overhead mechanical stirring.

13. Anhydrous ethanol (<0.005% water) was purchased from Aldrich Chemical Company, Inc. and used as received.

14. Lithium tri-*tert*-butoxyaluminum hydride (1.0M in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc. and used as received.

15. Rochelle's salt solution was prepared by dissolving potassium sodium tartrate (30 g) and potassium carbonate (3.0 g) in 270 mL of water.

16. The enantiomeric excess of the epoxide **4** was >99% by chiral HPLC. Conditions: Chiralcel OD NP, 250 x 4.6 mm, 10 μm particle size, solvent (isocratic) 98% heptane, 1% methanol, 1% ethanol, flow rate 1.0 mL/min. Retention times were: *(R,R)*-epoxide, 10.2 min; *(S,S)*-epoxide (**4**), 11.0 min. Compound **4** had the following properties: mp (DSC) 125 °C. $[\alpha]_D^{25}$ -8.3 (c = 1.00, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9 H), 2.75 (br m, 1 H), 2.80 (m, 1 H), 2.87 (m, 1 H), 2.95 (m, 2 H), 3.69 (m, 1 H), 4.46 (br s, 1 H), 7.2–7.4 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 37.5, 46.7, 52.5, 53.2, 79.5, 126.6, 128.4, 129.4, 137.7, 155.2. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.44; H, 8.19; N, 5.30.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

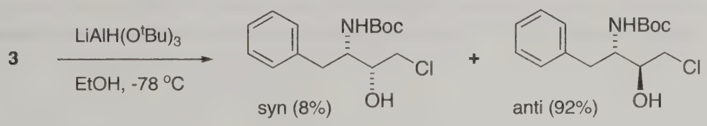
3. Discussion

N-Protected α-amino epoxides are broadly useful synthetic intermediates and in particular are ideal precursors for the hydroxyethylamine class of protease inhibitors. These compounds are frequently synthesized by one-carbon homologation of α-amino acids using diazomethane.[2] There are significant hazards associated with the use of diazomethane since this gaseous reagent is highly toxic, shock-sensitive, and explosive.[3] The procedure reported here, which is based on an earlier synthesis of α-fluorinated chloroketones,[4] was developed to provide an alternative to the use of diazomethane.[5]

Efficient reaction of Corey's reagent, dimethylsulfoxonium methylide,[6] with esters requires an electron-withdrawing group adjacent to the carbonyl, provided in the case of **1** by the α-BOC-amino substituent. Several examples of chloroketone synthesis via this method are shown in the Table. Esters of simple aliphatic acids react only sluggishly. In the presence of a suitable activating group, methyl esters as well as *p*-nitrophenyl esters will react. However, for substrates that are subject to epimerization such as **1**, the more reactive aryl ester is needed to preclude partial racemization.

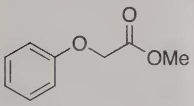
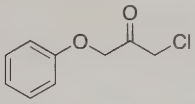
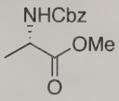
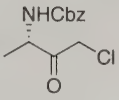
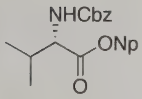
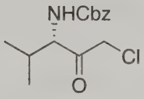
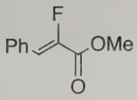
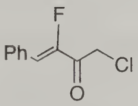
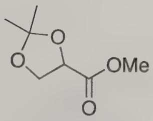
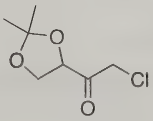
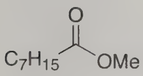
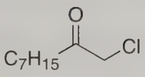
Our earlier procedure[5] for reduction of chloroketone **3** utilized sodium borohydride as the reductant. With that reducing agent, the *anti/syn* selectivity was only 4:1, necessitating the isolation and crystallization of the intermediate β-chlorohydrin prior to epoxide ring-closure. The current procedure takes advantage of Hoffman's report[7] that high *anti*-selectivity could be achieved with related substrates using lithium tri-*tert*-butoxyaluminum hydride in ethanol. This protocol improved selectivity for reduction of **3** to 92:8 (*anti/syn*). The intermediate β-chlorohydrins underwent epoxide ring-closure during work-up with the basic Rochelle salt solution. The desired *anti* isomer **4** was isolated from the mixed diastereomers via a simple crystallization. The Rochelle's salt solution also served to sequester the aluminum-containing co-products, simplifying the extractive workup.

As an alternative to this "telescoped" procedure, it is also possible to isolate the β-chlorohydrin intermediate. This is accomplished by replacing the Rochelle salt solution with water during the extractive work-up.[5] The β-chlorohydrin is recovered as a mixture of diastereomers as shown below. The pure *anti*-diastereomer is a crystalline solid (mp 122 °C) and can be isolated by crystallization from hot ethyl acetate.[5]



The best method for this reduction step varies depending on the nature of the α-chloroketone. When the chloroketone is prepared from an α-amino acid with a sterically large R group (e.g., valine), simple borohydride reduction provides high diastereoselectivity.[8] When the R group is small (e.g., alanine), hydrogenation using a “matched” ruthenium-BINAP catalyst is advantageous.[5] For asymmetric reduction of achiral chloroketones, the Noyori catalytic transfer hydrogenation procedure is recommended.[9] It should also be noted that, depending on which enantiomer of the Noyori catalyst is employed, this procedure can also be used to convert **3** into *either* the *syn* or the *anti* β-chlorohydrin, in each case with 90:10 diastereoselectivity.[10] In cases where the final epoxide is not crystalline, it will generally be desirable to isolate and crystallize the intermediate β-chlorohydrin.

Table. Synthesis of Chloroketones by One-Carbon Homologation of Esters

Ester	α-Chloroketone	Equiv/time/temp[a]	Yield (%)[b]	Ref.
		3/16/25	63[c]	5
		3/4/0	68[c]	5
		5/4/0	74[d]	5
		1/2/15	54	4
		3/16/25	71[e]	11
		5/72/0	25[f]	5

a) Reaction conditions: equiv of dimethylsulfoxonium methylide, time (h), temperature (°C).
b) Combined yield for ylide formation and HCl cleavage steps. c) Reagent generated from trimethylsulfoxonium chloride; other cases use the iodide. d) Yield after flash chromatography.
e) Cleavage step carried out with pyridinium hydrochloride (70 °C, 3 h) rather than HCl.
f) Yield for sulfur ylide step after flash chromatography; not converted to chloroketone.

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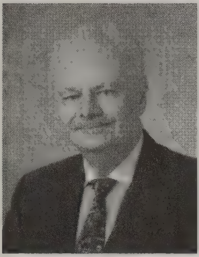
11. Wang, D.; Nugent, W. A., unpublished results.

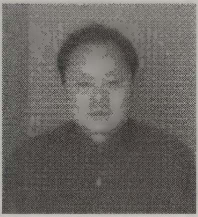
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Trimethylsulfoxonium iodide; (1774-47-6)
Boc-L-phenylalanine 4-nitrophenyl ester: L-Phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-, 4-nitrophenyl ester; (7535-56-0)
Dimethylsulfoxonium (*S*)-2-oxo-3-(Boc-amino)-4-phenylbutylide: Sulfoxonium, dimethyl-, (*3S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-4-phenylbutylide: (400611-25-8)
(*S*)-1-Chloro-3-(Boc-amino)-4-phenyl-2-butanone: Carbamic acid, [(*1S*)-3-chloro-2-oxo-1-(phenylmethyl)propyl]-, 1,1-dimethylethyl ester; (102123-74-0)
Lithium tri-*tert*-butoxyaluminum hydride; (17476-04-9)

(*2S,3S*)-1,2-Epoxy-3-(Boc-amino)-4-phenylbutane: Carbamic acid, [(*1S*)-1-(*2S*)-oxiranyl-2-phenylethyl]-, 1,1-dimethylethyl ester; (98737-29-2)



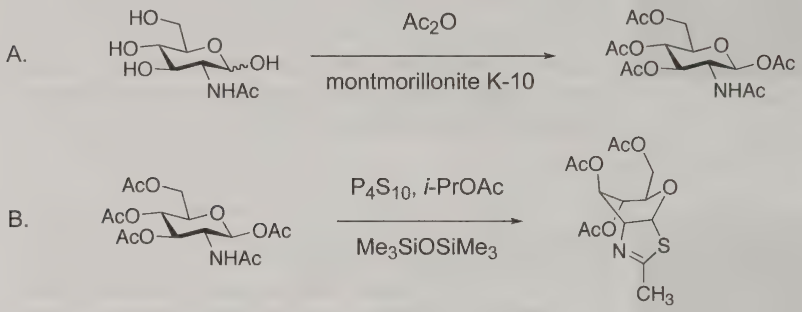
William A. Nugent received his B. S. in Chemistry from Purdue University in 1969. After three years of teaching high school chemistry, he returned to Indiana University to earn his Ph. D. under the direction of Prof. Jay K. Kochi. In 1976 he joined the Central Research Department of the DuPont Company, later moving to the DuPont Pharmaceutical Company. Bristol-Myers Squibb subsequently acquired the DuPont Pharmaceutical Company and Bill currently holds the position of Senior Research Fellow at BMS. His principal research interest is the application of homogeneous catalysis in pharmaceutical manufacture.



Dengjin Wang was born in China in 1958. He received his B.S. degree from Nanjing University in 1982 and M.S. degree in 1987. In 1997, he joined DuPont-Merck Pharmaceuticals in the Department of Process Research and Development, where he worked on the development of anti-HIV agents. In 2001, he joined Bristol-Myers Squibb under the supervision of Dr. William Nugent. His research interests include catalysis and asymmetric reactions for C-C and C-N bond formation, as well as the development of practical processes for the large-scale production of active pharmaceutical ingredients and bioactive building blocks.

Jason Kowal earned an A.A.S degree in Chemical Technology in 1994 from Erie County Community College North Buffalo, New York followed by a B.S degree in Medicinal Chemistry in 1997 from State University of New York at Buffalo where his research began under Michael R. Detty, and finished under David G. Hangauer. Jason has been employed at Merck & Co., Inc. Process Research since 1997 and is currently a Research Chemist responsible for the development and implementation of new and efficient syntheses of novel active pharmaceutical ingredients from milligram to gram laboratory scale, to multi kilo bulk preparatory lab deliveries for clinical study, to pilot plant production.

THIONATION: GlcNAc-THIAZOLINE TRIACETATE {(3a*R*,5*R*,6*S*,7*R*,7a*R*)-5-ACETOXYMETHYL-6,7-DIACETOXY-2-METHYL-5,6,7,7a-TETRAHYDRO-3a*H*-PYRANO[3,2-*d*]THIAZOLE}



Submitted by Spencer Knapp, Richard A. Huhn, and Benjamin Amorelli.[1]
Checked by Erikah E. Englund and Peter Wipf.[2]

1. Procedure

Caution! The following operations produce lachrymatory and corrosive vapors and should be carried out in a well-ventilated fume hood.

A. 2-Acetamido-2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-glucopyranose. A dry, 2000-mL, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (41 × 19 mm) and an ice-salt bath, and at the respective necks with a thermometer, a septum, and a rubber stopper. A nitrogen atmosphere is incorporated by a needle inserted through the septum. The stopper is temporarily removed, replaced with a funnel and acetic anhydride (900 mL, 9.52 mol, Note 1) is added from a bottle that had been stored in a refrigerator at 5 °C. The stopper is replaced and the acetic anhydride is cooled to 0 °C (internal temperature) with stirring, the stopper is again replaced by a funnel, and then 80.0 g (362 mmol) of *N*-acetyl-D-glucosamine and 270 g of montmorillonite K-10 (Note 1) are sequentially added over a 10-min period such that the internal temperature does not rise above ambient. The stopper is replaced, the ice bath is removed, and the suspension is stirred for 24 h.

Org. Synth. **2007**, *84*, 68-76
Published on the Web 11/1/06

The reaction mixture is filtered through a medium porosity sintered glass funnel (600 mL capacity) pre-coated with a pad of 20 g of Celite moistened with methyl acetate (Note 1). The flask and filtered solids are washed with methyl acetate, about 1 L total, and then the combined filtrate is concentrated on a rotary evaporator (40 °C, 5 mmHg). The resulting orange residue is dislodged with a spatula, and then dissolved in 200 mL of hot methanol. The methanolic solution is placed in a 5 °C explosion proof refrigerator and a precipitate forms over 24 h. The solid is collected by filtration and washed with 100 mL of diethyl ether, then dried (23 °C, 1 mm) to afford 46.3 g (33%) of product as a white solid (mp 179–180 °C) (Notes 2 and 3).

B. *GlcNAc-thiazoline triacetate.* A 1000-mL, two-necked, round-bottomed flask under a nitrogen atmosphere immersed in an oil bath is fitted with Teflon-coated magnetic stir bar (41 × 19 mm), a rubber septum and a reflux condenser capped with a septum, through which nitrogen is affixed by use of a needle. The septum on the flask is temporarily removed, a funnel inserted and the vessel is charged with 300 mL of isopropyl acetate and 18.3 g (40 mmol) of phosphorus pentasulfide (P_4S_{10}). The resulting suspension is stirred rapidly while 76.3 mL (360 mmol) of hexamethyldisiloxane (Note 4) is added via syringe over a 5-min period. The mixture is heated at reflux for 10 min while vigorous stirring is maintained. The solution is allowed to cool to just below reflux, the septum on the flask is replaced with a funnel and 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (40.0 g, 103 mmol) is added in four portions with continuous stirring over a 5-min period. The septum is replaced and the reaction mixture is then brought back to reflux, and held at that temperature for 2–3 h, during which period it becomes homogeneous and orange. TLC analysis (3:1, dichloromethane / ethyl acetate) indicates complete conversion to product ($R_f = 0.40$ on silica).

The reaction mixture is allowed to cool to room temperature and then stirred for an additional 12 h (Note 5). The septum is removed and acetone (150 mL) is added. The flask is cooled to 0 °C in an ice-salt bath (Note 6), and then 52 mL of 5.3 M aqueous K_2CO_3 is added. The quenched reaction mixture is stirred at 0 °C for 30 min, then water and isopropyl acetate are used to transfer the reaction mixture to a 2-L separatory funnel (total 300 mL of water and 200 mL of isopropyl acetate). The organic layer is separated and washed with 0.53 M aqueous K_2CO_3 (3 × 200 mL or until the aqueous layer is colorless), and then dried over 30 g of anhydrous magnesium sulfate. Filtration followed by concentration on the rotary evaporator (23 °C, 5 mmHg) gives an orange oil, which is mixed with 50 mL of isopropyl acetate and 55 g of silica, and then concentrated to give an orange powder. A plug of 170 g of silica moistened with isopropyl acetate is layered onto a coarse porosity sintered glass funnel (600 mL capacity). The orange powder is placed on the silica plug and tamped with a piece of filter paper, which is left in place. A mixture of heptanes / isopropyl acetate (70:30, 1.25 L, then 40:60, 125 mL) is used to wash through high R_f impurities, which are discarded as waste. Elution with 1.5 L of 40:60 heptanes / isopropyl acetate is followed by pure isopropyl acetate (~1 L) until the product is washed off the silica according to TLC analysis. Concentration of this latter solution on the rotary evaporator (23 °C, 5 mmHg) followed by a high vacuum (27 °C, 0.05 mmHg), until a constant weight is obtained, provides 31.1 g (88%) of GlcNAc-thiazoline triacetate as an orange oil (Note 7).

Notes

1. Acetic anhydride, *N*-acetyl-D-glucosamine, and montmorillonite K-10 were purchased from Aldrich Chemical Company, Inc., and are used as received. All solvents throughout this procedure were reagent grade and were used as received. The submitters report that a nitrogen atmosphere is not required for the reaction, for similar results are obtained in the absence of a nitrogen atmosphere.

2. Lit. mp 187 °C (ethanol),[3] 185–186 °C (water),[4] 186–186.5 °C (methanol/ether),[5] 188–189 °C (ethanol, repeated).[6]

3. The product was >99% pure according to ^{1}H NMR analysis. The α-anomer, when present, gives a signal in the ^{1}H NMR spectrum at δ 6.17 (d, *J* = 3.2 Hz, 1 H). The spectral properties of the β-pentaacetate are as follows: $[\alpha]_D^{20}$ 7.2 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1} 3257, 3074, 1747, 1656, 1555, 1444, 1370, 1220, 1069; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.93 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 3.81 (ddd, *J* = 2.4, 4.5, 9.0 Hz, 1 H), 4.12 (dd, *J* = 2.1, 12.5 Hz, 1 H), 4.27 (dd, *J* = 4.6, 12.6 Hz, 1 H), 4.26–4.35 (m, 1 H), 5.09–5.17 (m, 2 H), 5.56 (d, *J* = 9.5 Hz, 1 H), 5.69 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.5, 20.6, 20.7, 20.8, 23.1, 53.1, 61.7, 67.8, 72.6, 72.9, 92.6, 169.2, 169.5, 170.1, 170.6, 171.2; MS *m/z* (relative intensity) 413 (13), 412 (100, $[M+Na]^+$), 353 (5), 352 (40), 330 (3); HRMS Calcd for $C_{16}H_{23}NO_{10}Na$ (M+Na) 412.1220, Found 412.1216; Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95. Found: C, 48.98; H, 5.79.

4. Phosphorus pentasulfide and hexamethyldisiloxane were purchased from Aldrich Chemical Company, Inc., and used as received. The submitters utilized a drying tube as opposed to the nitrogen atmosphere and obtained similar results.

5. Cleaner reaction mixtures were obtained when the reaction mixture was allowed to rest for an additional period after reflux.

6. At quench temperatures higher than 0 °C, some hydrolysis of product during the carbonate treatment was observed by TLC.

7. The product was >95% pure according to ^{1}H NMR analysis. The spectral and analytical properties are as follows: $[\alpha]_D^{20}$ –28.3 (*c* 0.4, $CHCl_3$); IR (neat) cm^{-1} 3308, 2958, 1747, 1629, 1433, 1371, 1232, 1040; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.08 (s, 6 H), 2.13 (s, 3 H), 2.31 (d, *J* = 2.3 Hz, 3 H), 3.53 (dt, *J* = 9.5, 4.2 Hz, 1 H), 4.11 (app d, *J* = 4.1 Hz, 2 H), 4.44–4.48 (m, 1 H), 4.95 (dt, *J* = 9.5, 1.6 Hz, 1 H), 5.56 (dd, *J* = 1.7, 3.3 Hz, 1 H), 6.23 (d, *J* = 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.5, 20.6, 20.7, 20.8, 63.2, 68.3, 69.2, 70.5, 76.5, 88.6, 168.2, 169.2, 169.5, 170.5; MS *m/z* (relative intensity): 346 (9), 345 (23, $[M]^+$), 312 (15), 286 (29), 285 (24), 272 (25), 225 (25), 183 (26), 166 (44), 165 (100), 152 (53), 141 (60); HRMS Calcd for $C_{14}H_{19}NO_7S$ 345.0882; Found 345.0878; Anal. Calcd for $C_{14}H_{19}NO_7S$: C, 48.69; H, 5.55; N, 4.06; S, 9.29. Found: C, 48.44; H, 5.68; N, 4.00; S, 9.26.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

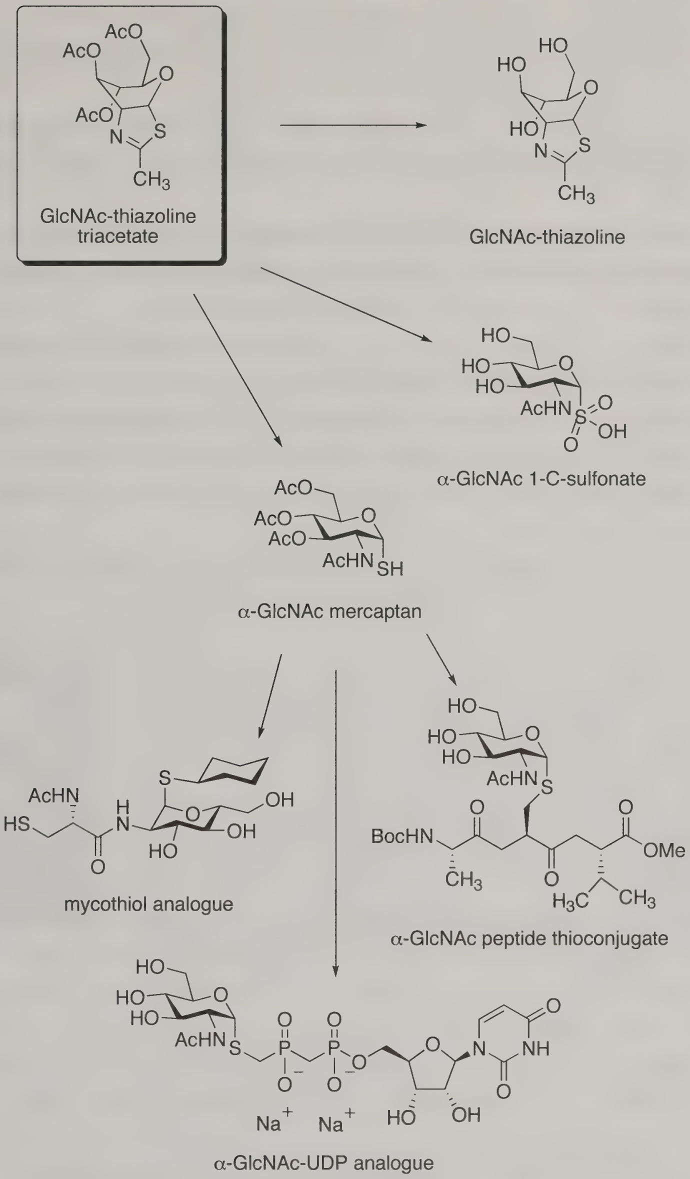
3. Discussion

The preparation of 2-acetamido-2-deoxy-tetra-*O*-acetyl-β-D-glucopyranose is based on the report by Bhaskar and Loganathan[7] that describes the use of montmorillonite K-10 clay as an acidic catalyst for per-*O*-acetylation of sugars. The conditions have been modified to facilitate scale-up and isolation of pure β-anomer. This product has most commonly been made from D-glucosamine by a four-step route involving the intermediacy of an *N*-(*p*-methoxybenzylidene) derivative,[3] and by acetylation with anhydrous zinc(II) chloride as promoter.[4] In our hands neither procedure proved as convenient on the 0.1 mole scale as the present one. The β-peracetate may also obtained commercially from Aldrich Chemical Company ($87 for 5 g in 2005).

GlcNAc-thiazoline triacetate may be synthesized from 2-acetamido-2-deoxy-tetra-*O*-acetyl-β-D-glucopyranose in quantitative yield on a 2 g scale by using freshly prepared Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, followed by column chromatography.[8] The corresponding GalNAc-thiazoline triacetate has been synthesized analogously.[9] The thionation/cyclization reaction described herein is based on the P_4S_{10}/hexamethyldisiloxane procedure of Curphey,[10] which minimizes the formation of P/S byproducts that must be removed chromatographically. The amount of P_4S_{10} relative to starting material is increased to 0.4 equivalents in this procedure to accommodate the thionation of the byproduct, acetic acid, and to ensure that the reaction runs to completion.

GlcNAc-thiazoline triacetate has been hydrolyzed to the corresponding triol (Scheme 1), which is an effective inhibitor[11] and mechanistic/structural probe [12,13,14,15] of a family of 20 *N*-acetylhexosaminidases and related enzymes.[16,17,18] Alternatively, hydrolysis of the thiazoline ring gives the α-mercaptan stereoselectively,[8] and this has been used in turn to prepare α-GlcNAc thioconjugates,[8,19] including glycopeptide analogues,[20,21] mycothiol analogues,[22,23] and α-GlcNAc-UDP analogues.[24] Oxidation of the thiazoline in the presence of ethanol leads to the α-GlcNAc 1-C-sulfinate and 1-C-sulfonate *O*-ethyl esters.[25]

Scheme 1



1. Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey, Piscataway, NJ 08554-8087, USA.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA

15260, USA.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Acetic anhydride; (108-24-7)

N-Acetyl-D-glucosamine: D-Glucose, 2-(acetylamino)-2-deoxy-; (7512-17-6)

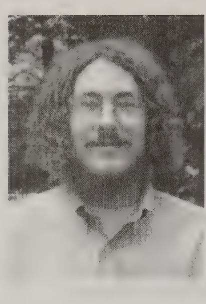
2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose: β-D-Glucopyranose, 2-(acetylamino)-2-deoxy-, 1,3,4,6-tetraacetate; (7772-79-4)

Phosphorus pentasulfide; (1314-80-3)

GlcNAc-thiazoline triacetate. (3a*R*,5*R*,6*S*,7*R*,7a*R*)-5-Acetoxymethyl-6,7-diacetoxy-2-methyl-5,6,7,7a-tetrahydro-3a*H*-pyrano[3,2-*d*]thiazole: 5*H*-Pyrano[3,2-*d*]thiazole-6,7-diol, 5-[(acetyloxy)methyl]-3a,6,7,7a-tetrahydro-2-methyl-, diacetate (ester), (3a*R*,5*R*,6*S*,7*R*,7a*R*)-; (67109-74-4)

Hexamethyldisiloxane; (107-46-0)

Spencer Knapp was born in Baytown, Texas, and raised in Tallmadge, Ohio. As a Fellow of the Ford Foundation Six-Year BA-PhD Program, he received his respective degrees in 1972 and 1975 from Cornell University, both under the mentorship of Jerrold Meinwald. Following an NIH Postdoctoral Fellowship with E. J. Corey, he joined the faculty of Rutgers University. His research interests include the synthesis of natural products, enzyme inhibitors, and complex ligands, and the development of new synthetic methods. He has received an NCI Young Investigator Award, an American Cyanamid Faculty Award, and a Hoechst-Celanese Innovative Research Award.

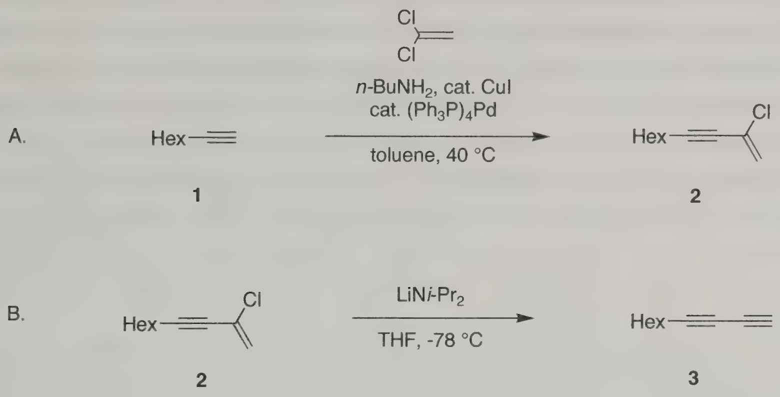


Richard Huhn was born in Providence, Rhode Island and was raised mostly in Chester, New Jersey. He received his bachelor's degree in 2005 with highest honors from Rutgers University, where he double-majored in chemistry and physics and worked in the laboratories of Professor Spencer Knapp. He is currently a graduate student working for Professor Stephen Buchwald in the chemistry department of the Massachusetts Institute of Technology. His interests include organometallic chemistry, computational chemistry, and mechanistic investigations into organic and organometallic processes.

Benjamin Amorelli was born in Livingston, New Jersey in 1974. He graduated from Rutgers University with a BS in Environmental Science in 1997 and was employed as a geologist until beginning graduate study in 1999 at Montclair State University, where he received a MS in chemistry. He is currently a Thomas Reid Graduate Fellow at Rutgers University under the guidance of Professor Spencer Knapp, and is interested in synthetic chemistry, molecular design, and the chemistry and biology of natural products.

Erikah E. Englund received her B.S. degree at the University of Wisconsin, Madison in 2001 and performed research under Prof. Steven Burke. She is currently pursuing her PhD degree at the University of Pittsburgh under the supervision of Prof. Peter Wipf. Her graduate studies have included the synthesis of palmarumycin analogues and the continuation of studies towards the total synthesis of the spiroxins.

SYNTHESIS OF TERMINAL 1,3-DIYNES VIA SONOGASHIRA COUPLING OF VINYLIDENE CHLORIDE FOLLOWED BY ELIMINATION. PREPARATION OF 1,3-DECADIYNE



Submitted by Amanda L. Kohnen and Rick L. Danheiser.[1]
Checked by Scott E. Denmark and Xiaorong Liu.

1. Procedure

A. *2-Chloro-1-decen-3-yne* (**2**). A 350-mL, round-bottomed pressure flask (Note 1) equipped with a magnetic stir bar, rubber septum, and argon inlet needle (Note 2) is charged with $(Ph_3P)_4Pd$ (3.46 g, 2.99 mmol, 0.03 equiv) (Note 3) and 150 mL of toluene (Note 4), and then vinylidene chloride (11.98 mL, 14.54 g, 150 mmol, 1.5 equiv) (Note 5) is added via syringe over 2 min. The resulting yellow mixture is stirred at room temperature for 20 min and then a mixture of 1-octyne (14.75 mL, 11.02 g, 100.0 mmol) (Note 6) and *n*-butylamine (14.82 mL, 10.97 g, 150 mmol, 1.5 equiv) (Note 7) is transferred into the reaction mixture via cannula over 5 min from a 50-mL, round-bottomed flask fitted with a septum and an argon inlet needle. The flask is rinsed with two 3-mL portions of toluene, which are transferred into the pressure flask by cannula. The septum is temporarily removed from the pressure flask and copper(I) iodide (0.571 g, 2.99 mmol, 0.03 equiv) (Note 8) is added in one portion. Material adhering to the sides of the pressure flask is rinsed into the reaction mixture with 5 mL of toluene.

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The pressure flask is then sealed under argon with a threaded Teflon cap and submerged in a preheated oil bath at 40 °C behind a safety shield. (Note 9) The color of the clear yellow solution darkens to red over 4 h. After 8 h (Note 10), the cloudy red mixture is allowed to cool to room temperature and then filtered through a medium frit sintered glass funnel to remove the precipitated ammonium salt. The solid is washed with 100 mL of hexanes, and the filtrate is concentrated by rotary evaporation (40 °C, 20 mmHg). The resulting red oil (28.0 g) is diluted with 20 mL of CH_2Cl_2 and concentrated onto 40 g of silica gel (40 °C, 16 mmHg, Note 11). The clumpy powder is transferred to a column (25 x 8 cm) of 600 g of silica gel (Note 11) and is eluted with hexanes. After elution with 1000 mL of hexanes, 50-mL fractions are collected. Fractions 6 to 20 are combined and concentrated by rotary evaporation (40 °C, 20 mmHg) to afford 12.80–12.97 g (75–76%) of the desired enyne as a yellow liquid (Note 12).

B. *1,3-Decadiyne* (**3**). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, a 125-mL pressure-equalizing addition funnel fitted with a rubber septum, and a Claisen adapter fitted with an argon inlet adapter and a rubber septum penetrated by the Teflon probe of a thermometer (Notes 2, 13) is charged via syringe with diisopropylamine (23.4 mL, 16.9 g, 167 mmol, 2.6 equiv) (Note 14) followed by 200 mL of THF (Note 15). The solution is cooled at 0 °C in an ice-water bath and *n*-butyllithium solution (2.39 M in hexanes, 67 mL, 160 mmol, 2.5 equiv) (Note 16) is added dropwise via the addition funnel over 15 min. The resulting yellow solution is stirred at 0 °C for 30 min and then cooled to –78 °C (internal temperature) in a dry ice-acetone bath with the surface of the reaction mixture approximately 3 cm below the level of the cold acetone. A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, glass stopper, and argon inlet adapter is charged via syringe with a solution of enynyl chloride **2** (11.0 g, 64.4 mmol, 1.0 equiv) in 80 mL of THF and cooled to –78 °C (external temperature). The solution of enynyl chloride is transferred via cannula into the solution of LDA at such a rate so as to maintain the internal temperature between –70 and –78 °C (Notes 17, 18). The 250-mL flask is washed with two 5-mL portions of THF and the washings are transferred by cannula to the flask containing the LDA. The reaction mixture, which immediately darkens to a reddish color, is allowed to stir at –78 °C for 5–10 min and then poured into a 1-L separatory funnel containing 100 mL of half-saturated NH_4Cl solution. The resulting mixture is diluted with 150 mL of pentanes and extracted with

100 mL of 10% HCl solution. The organic phase is washed with 10% HCl (2 x 100 mL) and the combined aqueous phases are back-extracted with pentanes (2 x 100 mL). The combined organic layers are washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (23 °C, 16 mmHg) to afford 9.40 g of a red liquid. This material is dissolved in 20 mL of CH_2Cl_2 and deposited onto 10 g of silica gel (Note 11) by rotary evaporation (23 °C, 16 mmHg). The resulting clumpy powder is transferred onto a column (12 x 8 cm) of 300 g of silica gel (Note 11) and is eluted with pentanes. Fractions 15 to 33 (50 mL each) are combined and concentrated under reduced pressure (23 °C, 16 mmHg) to provide 5.95–6.26 g (69–73%) of diyne **3** as an orange liquid (Note 19).

2. Notes

1. The 350-mL, threaded, heavy-walled, round-bottomed pressure vessel (142 mm length x 82.5 mm OD) was purchased from Chemglass, Inc. The vessel was equipped with a Teflon cap (thread size 15 mm). Carrying out the reaction in a sealed vessel minimized the loss of vinylidene chloride (bp 30–32 °C).

2. The apparatus was flame-dried under reduced pressure (0.08 mmHg) and then maintained under an atmosphere of argon during the course of the reaction.

3. Tetrakis(triphenylphosphine)palladium(0) (99.9%) was purchased from Strem Chemicals, Inc. and used as received. The catalyst was stored at –18 °C under argon and was weighed in the glove box. The submitters observed no difference in the yield of **2** when the catalyst was stored and transferred in a dry box.

4. Toluene was purified by pressure filtration under argon through activated alumina.

5. *Caution: Vinylidene chloride is light sensitive and highly susceptible to polymerization and peroxide formation.* Vinylidene chloride (99%) was purchased from Aldrich Chemical Company, Inc. and stored in the dark at 0 ºC under argon. To remove any polymers and autoxidation products, the reagent was purified immediately before use by filtration through alumina according to the following procedure. A jacketed glass column (46 cm x 2.5 cm) cooled with cold running water and equipped with a needle at the bottom was charged with 30 g of Activity I basic alumina (EM Science, 70-230 mesh). A flame-dried, 50-mL, two-necked pear-

shaped flask equipped with two rubber septa was flushed with argon and attached to the needle at the bottom of the alumina column. Vinylidene chloride (approximately 25 mL) was added to the column and an exit needle was attached to the other septum of the flask. Nitrogen pressure was then applied to the top of the column to drive the vinylidene chloride through the column into the flask.

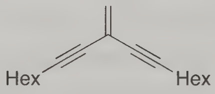
6. 1-Octyne (98%) was purchased from Alfa Aesar and used as received.

7. *n*-Butylamine (99.5%) was purchased from Aldrich Chemical Company, Inc. and purified by distillation at atmospheric pressure under argon from CaH_2.

8. Copper(I) iodide (98%) was purchased from Alfa Aesar and purified according to the following procedure. A 500-mL, round-bottomed flask was fitted with a Soxhlet extractor equipped with a reflux condenser fitted with a septum and argon inlet needle. The apparatus was flame-dried under vacuum (0.08 mmHg) and purged with argon. A Soxhlet thimble filled with 25 g of CuI was inserted into the extractor and 200 mL of THF was added via syringe. The extractor was wrapped with aluminum foil to shield the CuI from light and the THF in the flask was heated in an oil bath at reflux for 24 h. The apparatus was allowed to cool to room temperature and the CuI remaining in the thimble was transferred to a flame-dried, 100-mL, round-bottomed flask and dried at 0.08 mmHg for 24 h. The resulting CuI was ground up with a glass rod to afford a white, free-flowing powder.

9. The checkers submerged the flask such that the surface of the solution was 1 cm below the oil bath level. However, the checkers found that the oil level had no effect on the yield so long as good stirring was maintained.

10. The reaction was terminated when TLC analysis indicated that all of the octyne was consumed. TLC analysis was conducted using silica gel plates (elution with hexanes, visualization by UV and vanillin or $KMnO_4$); R_f values: octyne = 0.42, enyne product (**2**) = 0.55, bis-coupling product **4** = 0.30.



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11 Silica gel was purchased from Silicycle (230-400 mesh).

12. Enyne **2** is light sensitive and decomposes slowly at room temperature. This compound is best stored at 0 °C in the dark under argon. The product exhibits the following physical properties: $R_f = 0.55$ (hexanes); IR (neat) cm^{-1}: 2932, 2215, 1602, 1195; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, $J = 7.1$ Hz, 3 H), 1.28 – 1.33 (m, 4 H), 1.41 (app quint, $J = 7.1$ Hz, 2 H), 1.55 (app quint, $J = 7.3$ Hz, 2 H), 2.34 (t, $J = 7.1$ Hz, 2 H), 5.51 (s, 1 H), 5.55 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 14.3, 19.4, 22.7, 28.3, 28.7, 31.5, 77.7, 93.0, 120.6, 121.0. Anal. Calcd. for $C_{10}H_{15}Cl$: C, 70.37; H, 8.86. Found: C, 70.55; H, 8.84.

13. An Omegaette HH3087 mini-thermometer type K with a Teflon-coated thermocouple was used to monitor internal temperature.

14. Diisopropylamine (99.5%) was purchased from Aldrich Chemical Company, Inc. and distilled at atmospheric pressure under argon from CaH_2.

15. Tetrahydrofuran was purified by pressure filtration under argon through activated alumina.

16. *n*-Butyllithium was purchased from Alfa Aesar and titrated by the method of Watson and Eastham.[2]

17. The position of the exit needle of the cannula was adjusted so that it is at the level of the dry ice-acetone mixture in the external cooling bath. In this fashion, the solution of enynyl chloride ran down the cold wall of the flask approximately 3 cm above the surface of the solution of LDA. If the temperature of the reaction mixture rose above –70 °C, lower yields of diyne were obtained due to isomerization (see Discussion Section).

18. Approximately 20 min was required for the addition.

19. 1,3-Decadiyne was stored as a solution in pentanes at –20 °C under argon. The diyne exhibits the following physical properties: $R_f = 0.41$ (hexanes); IR (neat) cm^{-1}: 3310, 2957, 2298, 2226, 1466; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, $J = 7.0$ Hz, 3 H), 1.24–1.33 (m, 4 H), 1.38 (app quint, $J = 7.0$ Hz, 2 H), 1.53 (app quint, $J = 7.2$ Hz, 2 H), 1.96 (s, 1 H), 2.25 (t, $J = 7.0$ Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 14.2, 19.2, 22.7, 28.2, 28.7, 31.5, 64.6, 64.8, 68.7, 78.8. Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.11; H, 10.84.

Safety and Waste Disposal Information

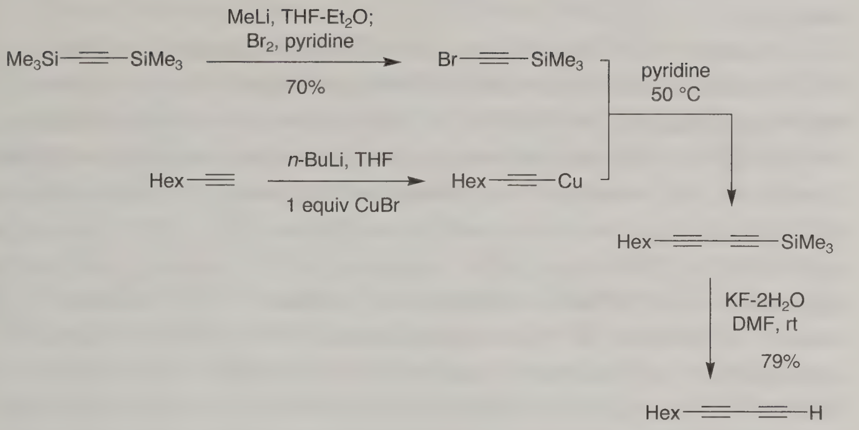
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

1,3-Diynes serve as valuable building blocks for the synthesis of natural products,[3] supramolecular constructs, and a variety of oligomeric alkynes and advanced materials with interesting electronic and optical properties. The most popular approaches to the synthesis of conjugated diynes involve alkynyl coupling reactions.[4] For example, the homocoupling of acetylenes can conveniently be achieved with copper catalysis using the Glaser reaction and its various modifications While unsymmetrical 1,3-diynes are available via the Cadiot-Chodkiewicz reaction,[6] the latter method involves the copper-catalyzed coupling of an alkyne with a 1-bromoalkyne; a variant of this process employs the coupling of alkynes with 1-haloalkynes in the presence of a combination of copper and palladium catalysts.[7,8] Several strategies have been developed for the synthesis of *terminal* 1,3-diynes based on the Cadiot-Chodkiewicz reaction. One approach employs the coupling of (bromoethynyl)trialkylsilanes followed by desilylation of the resultant 1-trialkylsilyl-1,3-diynes,[9] while an alternative strategy utilizes coupling reactions of propargylic alcohol derivatives followed by base-promoted fragmentation to unmask the terminal triple bond.[10,11] The application of the former approach to the preparation of the title compound, 1,3-decadiyne, has been reported by Zweifel[b] and is outlined in Scheme 1.[12]

While approaches such as this provide access to a variety of internal and terminal conjugated diynes, in many cases these coupling reactions are complicated by the formation of alkyne homodimers as significant byproducts. The cost of bis(trimethylsilyl)acetylene and the need for at least three synthetic operations further limits the attractiveness of this approach as a practical method for the synthesis of terminal diynes. These limitations have motivated the development of several alternative strategies for the preparation of terminal 1,3-diynes which are based on the Sonogashira coupling[13] of an alkyne with a dihaloethylene followed by b-elimination.

Scheme 1

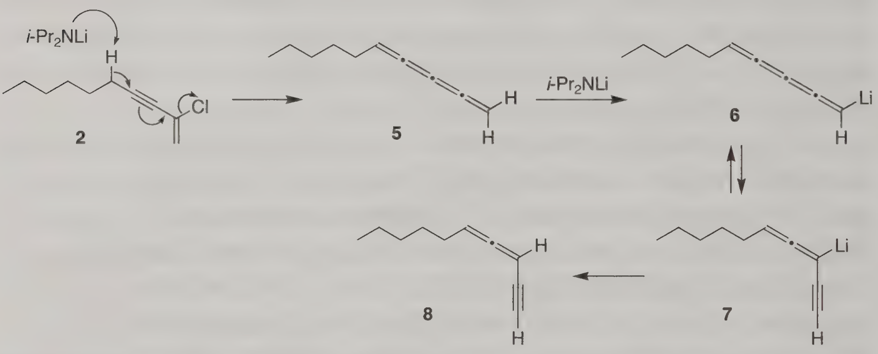


The selective mono-Sonogashira coupling of 1,2-dichloroethylene with alkynes was first demonstrated by Linstrumelle in 1981,[14] and subsequently several laboratories reported the synthesis of 1,3-diynes by Sonogashira coupling of various 1,2-dihaloethylenes followed by base-promoted dehydrohalogenation.[15] The requisite 1,2-dihaloalkenes are quite expensive, however, and Negishi[16] consequently introduced a more economical approach in 2003 based on the Sonogashira coupling of inexpensive 1,1-dichloroethylene (vinylidene chloride).[17]

The method of Negishi provides the basis for the optimized procedure described here for the synthesis of 1,3-decadiyne. In the case of the first step, the Sonogashira coupling of vinylidene chloride and 1-octyne, the catalyst loading has been reduced relative to the original Negishi protocol (from 5 to 3 mol% each for $(Ph_3P)_4Pd$ and CuI), and the amount of vinylidene chloride has been reduced from 5 to 1.5 equivalents. Our initial attempts to reduce the amount of vinylidene chloride below 5 equivalents were not successful. As the amount of vinylidene chloride was reduced, the octyne homodimer (7,9-hexadecadiyne) and enediyne **4** (the product of bis-coupling) appeared as major byproducts and the desired chloroenyne was obtained in greatly diminished yield. We hypothesized that the volatile vinylidene chloride (bp 30–32 °C) was escaping during the course of the reaction, and indeed, the formation of these byproducts could be minimized by simply carrying out the reaction in a sealed flask. Under the optimal conditions described here using 1.5 equiv of vinylidene chloride, the desired enyne was obtained in 75–76% yield and the crude coupling product was found to contain only 5-10% of enediyne **4** and less than 5% of the homodimer.

As reported by Negishi, exposure of enynyl chloride **2** to LDA at –78 °C effected β-elimination leading to the desired diyne **3**. We have noted that temperature control was critical to the success of this transformation, particularly when the reaction was conducted on scales greater than 500 mg. Specifically, the allenyne **8** was formed as a byproduct in yields of up to 40% if the reaction temperature was allowed to rise above –70 °C during the addition of the chloroenyne to the solution of LDA. Scheme 2 outlines the likely mechanism for the formation of this byproduct. 1,4-Elimination[18] of **2** leads to the tetraene **5**, which is further metalated by LDA to afford the organolithium intermediates **6** and/or **7**. Protonation then furnishes the allenyne **8**. The possibility that **8** arises from isomerization of 1,3-decadiyne was ruled out by control experiments that demonstrated that the diyne was not converted to **8** upon exposure to LDA under the conditions of the reaction.

Scheme 2



The formation of the allenyne byproduct could be minimized by carefully controlling the temperature of the reaction mixture, especially during the addition of the chloroenyne to LDA, which resulted in an exothermic reaction. Temperature control was best achieved by precooling the solution of chloroenyne in THF to –78 °C and employing a solution of less than 1.0 M concentration. The solution was added slowly at such a rate that the internal temperature of the reaction mixture did not exceed –70 °C. Under these conditions the diyne was obtained in 66–72% yield contaminated with <2% of the allenyne.

In summary, an improved protocol for the preparation of 1,3-decadiyne (**3**) by the method of Negishi has been developed. This approach employs the Sonogashira coupling of 1-octyne with vinylidene chloride followed by base-promoted dehydrochlorination with LDA. The optimized conditions described here provide 1,3-decadiyne in good yield on multigram-scale and are considerably more practical and efficient than previous methods reported for the preparation of this diyne.[19]

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139. Financial support by the National Institutes of Health (GM 28273) is gratefully acknowledged. A.L.K was supported in part by a Massachusetts Institute of Technology Leventhal Presidential Fellowship and by the American Council of Independent Laboratories.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

n-Butylamine: 1-Butanamine; (109-73-9)
1-Octyne; (629-05-0)
Vinylidene chloride: 1,1-Dichloroethene; (75-35-4)
2-Chloro-1-decen-3-yne; (534600-74-3)
Copper(I) iodide; (7681-65-4)

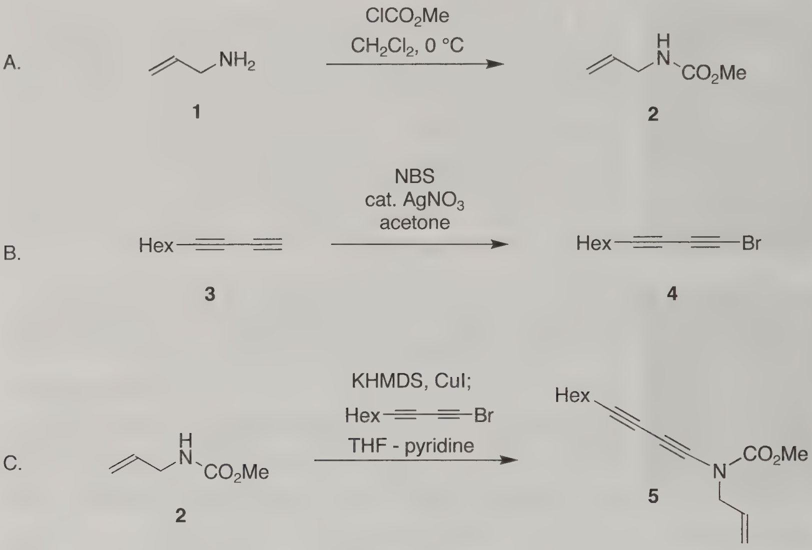
1,3-Decadiyne; (55682-66-1)
Diisopropylamine: *N*-(1-methylethyl)-2-propanamine; (108-18-9)

Rick L. Danheiser received his undergraduate education at Columbia where he carried out research in the laboratory of Professor Gilbert Stork. He received his Ph.D. at Harvard in 1978 working under the direction of E. J. Corey on the total synthesis of gibberellic acid. Dr. Danheiser is the A. C. Cope Professor of Chemistry at MIT where his research focuses on the design and invention of new annulation and cycloaddition reactions, and their application in the total synthesis of biologically active compounds.

Amanda L. Kohnen was born in 1981 in West Hollywood and grew up in Yuma, Arizona. She did her undergraduate work at the University of California, San Diego and received a B.S. degree in Chemistry in 2004. She is now pursuing graduate studies at the Massachusetts Institute of Technology where her research under the direction of Professor Rick Danheiser involves the development of new synthetic methods and the total synthesis of biologically active natural products. Ms. Kohnen is the recipient of an MIT Leventhal Presidential Fellowship, a Pfizer Research Fellowship, and an NSF Graduate Research Fellowship.

Xiaorong Liu graduated with BS and MS degrees in Chemistry from Nanjing University in China where she carried out research on the synthesis of organic conducting polymers in the laboratory of Professor Xue Gi. In the fall of 1999, she began graduate studies under the direction of Professor Robert K. Boeckman, Jr. at the University of Rochester where her Ph.D. thesis focused on the total synthesis of (–)-Apoptolidin. In the fall of 2004, she joined the laboratory of Professor Denmark as a postdoctoral associate at University of Illinois at Urbana-Champaign.

SYNTHESIS OF YNAMIDES BY *N*-ALKYNYLATION OF AMINE DERIVATIVES. PREPARATION OF *N*-ALLYL-*N*-(METHOXYCARBONYL)-1,3-DECADIYNYLAMINE



Submitted by Amanda L. Kohnen, Joshua R. Dunetz, and Rick L. Danheiser.[1]
Checked by Scott E. Denmark and Xiaorong Liu.

1. Procedure

A. *N-(Methoxycarbonyl)-2-propenylamine* (**2**) (Note 1). A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, an argon gas inlet tube, a rubber septum, which is pierced with a Teflon-coated thermocouple, and a 200-mL pressure-equalizing addition funnel fitted with a rubber septum (Note 2) is charged via syringe through the septum with allylamine (**1**) (14.0 mL, 10.68 g, 187 mmol, 2.1 equiv) (Note 3) and 100 mL of dichloromethane (Note 4). The solution is cooled to 0 °C (internal temperature) in an ice-water bath and a solution of methyl chloroformate (7.0 mL, 8.6 g, 91 mmol) (Note 5) in 30 mL of dichloromethane is added dropwise via the addition funnel over 10 min. The resulting white mixture is allowed to warm to room temperature over 30 min and then transferred to a

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500-mL separatory funnel and extracted with 50 mL of aqueous 1M HCl solution, 50 mL of saturated aqueous $NaHCO_3$ solution, and 50 mL of saturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (23 °C, 16 mmHg) to afford 10.12–10.26 g (97–98%) of carbamate **2** as a colorless oil (Note 6).

B. *1-Bromo-1,3-decadiyne* (**4**). Into a 200-mL, round-bottomed flask equipped with a magnetic stir bar (Note 2) is added 1,3-decadiyne (**3**) (5.66 g, 42.2 mmol) and 100 mL of acetone (Note 7). The flask is equipped with a rubber septum and argon inlet needle. *N*-Bromosuccinimide (8.26 g, 46.4 mmol, 1.1 equiv) (Note 8) and $AgNO_3$ (0.717 g, 4.22 mmol, 0.10 equiv) (Note 9) are each added in one portion through temporary removal of the septum. The rubber septum is replaced with an argon inlet adapter, the flask is wrapped with aluminum foil (Note 10), and the reaction mixture is stirred at room temperature for 22 h (Note 11). The resulting cloudy orange mixture is transferred to a 500-mL separatory funnel with the aid of 100 mL of pentanes and washed with two 50-mL portions of saturated aqueous $Na_2S_2O_3$ solution (Note 12). The combined aqueous layers are extracted with two 50-mL portions of pentanes and the combined organic phases are washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (23 °C, 16 mmHg) to provide 8.18–8.25 g (91–92%) of bromodiyne **4** as a red oil (Notes 13, 14).

C. *N-(Methoxycarbonyl)-N-(2-propenyl)-1,3-decadiynylamide* (**5**). Into a 500-mL, three-necked, round-bottomed flask is weighed carbamate **2** (3.98 g, 34.6 mmol). The flask is equipped with a large magnetic stir bar, an argon inlet adapter, rubber septum, and a 125-mL pressure-equalizing addition funnel fitted with a rubber septum (Note 1). Tetrahydrofuran (130 mL) (Note 15) and pyridine (70 mL, 68.0 g, 867 mmol, 25 equiv) (Note 16) are added via syringe through the septum. The solution is cooled to 0 °C (internal temperature) in an ice-water bath and 38 mL of potassium hexamethyldisilazide solution (0.91 M in THF, 34.6 mmol, 1.0 equiv) (Note 17) is added via syringe over 10 min. The peach-colored slurry is allowed to warm to room temperature over 15 min and then copper(I) iodide (6.58 g, 34.6 mmol, 1.0 equiv) (Notes 18, 19) is added in one portion by temporarily removing the septum. The resulting yellow-green mixture is stirred at room temperature for 2 h. A solution of bromodiyne **4** (8.47 g, 39.8 mmol, 1.15 equiv) in 40 mL of THF is then added via the addition funnel over 45 min (5 mL THF rinse) (Note 20). The flask and addition funnel are wrapped with aluminum foil to protect the bromodiyne **4** from light and the resulting mixture is stirred at room temperature for 20 h (Note 21). The dark red-brown reaction mixture is transferred to a 1-L separatory funnel, diluted with 150 mL of diethyl ether, and washed with four 100-mL portions of a 3:1 mixture of saturated NaCl solution and concentrated NH_4OH solution (Note 22). The blue aqueous layers are extracted with two 100-mL portions of Et_2O, and the combined organic layers are washed with two 200-mL portions of 1M HCl solution, 200 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (40 °C, 16 mmHg) to afford 18.5 g of dark red oil. This material is transferred to a column (12 x 8 cm) of 300 g of silica gel and eluted with 500 mL of hexanes. Elution is then continued with 5% EtOAc-hexanes and 50-mL fractions are collected. Fractions 14 to 51 are combined and concentrated by rotary evaporation (23 °C, 16 mmHg) to provide 6.88 g (80%) of diynamide **5** as a red oil (Notes 23, 24).

2. Notes

1. *t*-Butyl and ethyl *N*-allylcarbamate are commercially available. The method described here for the synthesis of the methyl derivative **2** illustrates a general procedure for the preparation of carbamates which usually delivers the desired compounds in near-quantitative yield and in a state of high purity, suitable for use in the *N*-alkynylation reaction without further purification.

2. The apparatus was flame-dried under reduced pressure (0.08 mmHg) and then maintained under an atmosphere of argon during the course of the reaction.

3. Allylamine (98%) was purchased from Alfa Aesar and used without purification.

4. Dichloromethane was purified by pressure filtration under argon through activated alumina.

5. Methyl chloroformate (99%) was obtained from Aldrich Chemical Company, Inc. and used as received.

6. The product exhibits the following spectroscopic properties: R_f = 0.17 (hexanes/EtOAc, 4/1); IR (neat) cm^{-1}: 3337, 3084, 2952, 1702, 1534; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.68 (s, 3 H), 3.81 (app s, 2 H), 4.73 (br s, 1 H), 5.13 (dd, J = 10.2, 1.2 Hz, 1 H), 5.19 (dd, J = 17.1, 1.2 Hz, 1 H), 5.84 (ddt, J = 17.1, 10.5, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 43.6, 52.4,

116.2, 134.7, 157.1. MS (EI) *m/z* 115 (M^+, 91), 100 (100). Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.77; H, 7.89; N, 11.89.

7. 1,3-Decadiyne was prepared via the *Organic Syntheses* procedure directly preceding this procedure. Acetone (99.5%) was purchased from Aldrich Chemical Company and was used as received.

8. *N*-Bromosuccinimide (NBS) (99%) was purchased from Aldrich Chemical Company, Inc. and purified by recrystallization from water according to the following procedure.[2] A 500-mL Erlenmeyer flask equipped with a magnetic stir bar was charged with NBS (30 g, 169 mmol) and 300 mL of deionized water and heated on a hot plate until the yellow mixture became homogeneous (approximately 90 °C). The resulting dark orange solution was cooled in an ice bath over 3 h and the white crystals that formed were collected by vacuum filtration on a Büchner funnel, washed with 100 mL of water, and then dried over P_2O_5 in a vacuum dessicator at 22 mmHg for 12 h to afford 21.2 g of NBS as white crystals.

9. Silver(I) nitrate (99.9%) was obtained from Alfa Aesar and used as received.

10. The reaction mixture was shielded from light due to the photosensitivity of NBS and bromodiyne **4**.

11. The progress of the reaction was monitored by thin layer chromatography. TLC analysis was conducted using silica gel plates (elution with hexanes, visualization by UV and vanillin); R_f values: diyne **3** = 0.41, bromodiyne **4** = 0.49.

12. Washing with saturated sodium thiosulfate solution removed traces of bromine.

13. The product exhibits the following spectroscopic properties: R_f = 0.49 (hexanes); IR (neat) cm^{-1}: 2956, 2930, 2858, 2141, 1466; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.1 Hz, 3 H), 1.24–1.32 (m, 4 H), 1.38 (app quint, J = 7.1 Hz, 2 H), 1.52 (app quint, J = 7.2 Hz, 2 H), 2.24 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 19.2, 22.7, 28.2, 28.7, 31.4, 37.0, 65.5, 65.9, 77.7. Anal. Calcd. for $C_{10}H_{13}Br$: C, 56.36; H, 6.15. Found: C, 56.35; H, 6.29.

14. In contrast to many other alkynyl bromides we have worked with, the bromodiyne **4** does not exhibit lachrymatory properties. As with all alkynyl halides, however, we nonetheless recommend avoiding any skin contact with this compound and carrying out all operations in a fume hood.

15. Tetrahydrofuran was purified by pressure filtration through activated alumina under argon.

16. Pyridine was purchased from Aldrich Chemical Company and purified by distillation under argon from CaH_2. The submitters found that lower yields were obtained in these coupling reactions if pyridine (Alfa Aesar, 99%, 0.1% water content) from a freshly opened bottle was used instead (see Discussion Section).

17. Potassium hexamethyldisilazide solution was purchased from Alfa Aesar and used as received. KHMDS in toluene (0.5 M, Aldrich) can be employed with similar results.

18. Copper(I) iodide (98%) was purchased from Alfa Aesar and purified according to the following procedure. A 500-mL, round-bottomed flask was fitted with a Soxhlet extractor equipped with a reflux condenser fitted with a rubber septum and argon inlet needle. The reaction apparatus was flame-dried under vacuum (0.08 mmHg) and purged with argon. A Soxhlet thimble filled with 25 g of CuI was inserted into the extractor and 200 mL of THF was added via syringe. The extractor was wrapped with aluminum foil to shield the CuI from light and the THF was heated in an oil bath at reflux for 24 h. The apparatus was allowed to cool to room temperature and the CuI was transferred to a flame-dried, 100-mL, one-necked, round-bottomed flask and dried at 0.08 mmHg for 24 h. The resulting CuI was ground up with glass rod to afford a white, free-flowing powder, which was stored under argon shielded from light.

19. The yield of ynamide product in a related coupling reaction was unchanged when CuI was used as received without purification.

20. Increasing the rate of addition resulted in reduced yields (see Discussion Section).

21. The progress of the reaction was monitored by thin layer chromatography. TLC analysis was conducted using silica gel plates (elution with 20% EtOAc-hexanes, visualization by UV and vanillin or $KMnO_4$); R_f values: bromodiyne **4** = 0.69, carbamate **2** = 0.17, diynamide **5** = 0.48.

22. The aqueous phase in the fourth wash should be colorless. Extraction of copper salts from the organic phase was found to be important in order to obtain the ynamide product in good yield.

23. The yield of ynamide varied from 73–80% in several runs carried out between one-half-scale and the scale described here.

24. The product exhibits the following spectroscopic properties: R_f = 0.48 (hexanes/EtOAc, 4/1); IR (neat) cm^{-1}: 2956, 2261, 2170, 174, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H), 1.23–1.32 (m, 4 H),

1.38 (app quint, $J = 7.2$ Hz, 2 H), 1.52 (app quint, $J = 7.1$ Hz, 2 H), 2.29 (t, $J = 7.1$ Hz, 2 H), 3.82 (s, 3 H), 4.05 (d, $J = 6.1$ Hz, 2 H), 5.25 (dd, $J = 1.2$, 10.3 Hz, 1 H), 5.29 (dd, $J = 1.3$, 17.3 Hz, 1 H), 5.85 (ddt, $J = 6.0$, 10.3, 18.8 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 14.3, 19.8, 22.7, 28.5, 28.7, 31.5, 52.7, 54.5, 58.0, 64.3, 67.5, 84.3, 119.3, 131.3, 155.9; MS (EI) *m/z*: 247 (M^+, 100). Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.59; H, 8.40; N, 5.31.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

In recent years, ynamides have emerged as exceptionally useful building blocks for organic synthesis.[3] Considerably more robust than simple ynamines, ynamides are more easily stored and handled, and more resistant to hydrolysis and polymerization. Ynamides tolerate a variety of reaction conditions incompatible with simple ynamines and have thus proved to be versatile substrates for a variety of synthetic transformations. Recent representative examples include Pauson-Khand reactions,[4] thermal and metal-promoted [4 + 2] cycloadditions,[5] [2 + 2 + 2] cyclotrimerizations,[6] Heck and other carbometalation reactions,[7] ring-closing metatheses,[8] radical-π cyclizations,[9] Pt-catalyzed cycloisomerizations,[10] ketene [2 + 2] cycloadditions,[11] and Pictet-Spengler-type cyclizations.[12]

Several strategies are available for the synthesis of ynamides.[3] While some success has been realized using the base-catalyzed isomerization of propargyl amides[13] and the dehydrohalogenation of halo enamides,[14] the most attractive approach to the synthesis of ynamides employs the direct *N*-alkynylation of amine derivatives. The first effective means for achieving this transformation was based on the addition of metalated amides to alkynyl(phenyl)iodonium salts.[15] Unfortunately, this method is subject to several serious limitations. While *sulfonamide* derivatives participate smoothly in these reactions, lactams, acyclic carbamates, and other carboxamide derivatives do not undergo alkynylation in good yield. Most significantly, this strategy can only be applied to the synthesis of ynamides in which the substituent on the alkynyl carbon is a hydrogen atom, or trialkylsilyl or aryl group.

Recent advances in copper-promoted coupling reactions of amine derivatives have provided the basis for a more general and efficient method that is applicable to the synthesis of a wide variety of ynamides. The preparation of diynamide **5** described here illustrates the method introduced by our laboratory in 2003 for the *N*-alkynylation of several classes of amine derivatives.[16] In our initial studies, we attempted to effect the coupling of carbamates with alkynyl halides using the conditions developed by Buchwald[17] for the amidation of aryl halides. Unfortunately, attempted application of Buchwald's catalyst system to the coupling of acyclic carbamates with 1-bromo-2-phenylacetylene gave only trace amounts of the desired ynamide, with the predominant product being the 1,3-diyne generated from "homocoupling" of the alkynyl halide. After considerable experimentation, success in effecting the desired alkynylation was finally achieved when we turned our attention to protocols in which complete conversion of the amide substrate to its copper derivative was carried out *prior* to addition of the alkynyl halide.[18] Under these conditions, the rate of alkynylation is significantly faster, copper-promoted dimerization of the alkynyl halide is greatly diminished, and the desired ynamides emerge as the major product of the reaction.

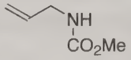
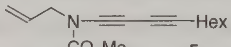
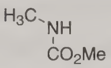
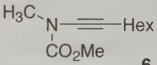
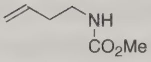
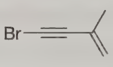
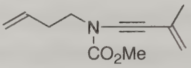
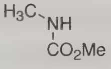
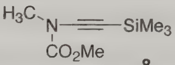
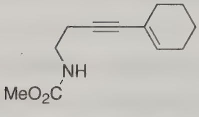
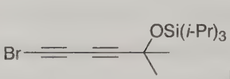
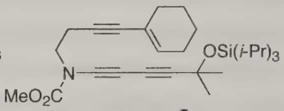
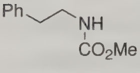
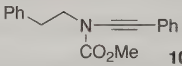
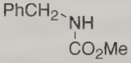
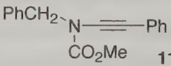
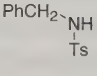
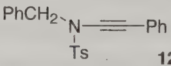
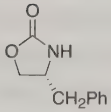
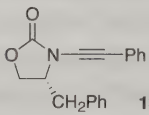
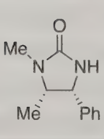
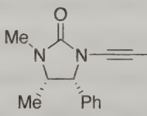
Both alkynyl bromides and alkynyl iodides participate smoothly in the desired reaction.[19] The procedure described here for the preparation of 1-bromo-1,3-decadiyne is based on the method of Hofmeister and coworkers[20] and provides the alkynyl bromide in near-quantitative yield and in a state of high purity. If extended storage is required, we recommend storing this compound as a solution in pentane at –20 °C.

The alkynylation procedure described here is a slightly modified version of our original protocol. As reported previously, a solution of the amide derivative is first deprotonated by reaction with 1 equiv of commercially available KHMDS (solution in THF) and then treated with 1 equiv of CuI. Somewhat diminished yields result if CuCN is employed in place of CuI. Although a full equivalent of CuI is required for the reaction, this salt is inexpensive and can be used as received without purification. After 2 h, the alkynyl bromide is added dropwise and the reaction is allowed to proceed at room temperature overnight. Slow addition of the bromide is important in minimizing the homocoupling side reaction. Only a slight excess of **4** (1.15 equiv) is employed in the optimal procedure described here, although in the case of other alkynyl bromides we occasionally found that the yield of coupling product is improved if 1.5 or even 2 equiv of the alkyne is employed. Originally we carried out the alkynylation reactions in a mixture of pyridine, benzene (from the alkynyl bromide stock solution), and THF (60:30:10 ratio by volume). In the optimized procedure described here, however, the amount of pyridine has been reduced to 25 equivalents, and the final solvent system consists of a mixture of THF and pyridine in a ratio of approximately 3:1.

The examples shown in Table 1 illustrate the scope of this method for the synthesis of ynamides. As reported previously, a broad range of alkynyl bromides participate in the reaction, including compounds that are especially prone to homocoupling such as halo derivatives of conjugated enynes and aryl acetylenes. Acyclic carbamates, sulfonamides, oxazolidinones, and cyclic ureas all undergo *N*-alkynylation in good yield. Significantly, the alkynylation reaction proceeds smoothly at room temperature, allowing its application to the synthesis of several classes of thermally sensitive ynamides, which are not available by other methods that require reaction at elevated temperature (vide infra).

Concurrent with our studies, Hsung and co-workers developed a complementary method for the synthesis of ynamides that also involves the coupling of amine derivatives with halo acetylenes. In 2003, Hsung reported that the copper catalyst system originally developed by Buchwald for the *arylation* and *vinylation* of amides, lactams, and carbamates[17] is also effective for the alkynylation of oxazolidinones and lactams.[21] The Hsung procedure requires reaction at elevated temperatures (110–150 °C) and employs catalytic CuCN in conjunction with a 1,2-diamine ligand in the presence of K_3PO_4. Unfortunately, under these conditions acyclic carbamates, sulfonamides, and cyclic ureas undergo alkynylation in poor yield. In 2004, Sato and co-workers reported a modified Buchwald protocol that is applicable to the alkynylation of acyclic and cyclic sulfonamide derivatives,[22] and the same year Hsung described a "second-generation catalyst system"[23] employing catalytic copper sulfate and 1,10-phenanthroline as ligand that is applicable to a broad range of amine derivatives including sulfonamides, imidazolidinones, and acyclic carbamates. This procedure does require reaction at elevated temperature (60–95 °C), however, and therefore is not applicable to the preparation of thermally sensitive ynamides. In the case of ynamide **5**, we found that the desired diynamide is produced in only 34–38% yield using the Hsung "second-generation" protocol as compared to 74–82% employing our room temperature procedure.

Table 1. Synthesis of Ynamides by Copper-Mediated N-Alkynylation

entry	amine derivative	alkyne	ynamide	yield (%)[a]
1[b]		$Br-C\equiv C-C\equiv C-Hex$	 **5**	82[c]
2[b]		$Br-C\equiv C-Hex$	 **6**	61[d]
3[b]			 **7**	68[d]
4[b]		$I-C\equiv C-SiMe_3$	 **8**	64[d]
5[f]			 **9**	51[e]
6[f]		$Br-C\equiv C-Ph$	 **10**	76[g]
7[f]		$Br-C\equiv C-Ph$	 **11**	63[d]
8[f]		$Br-C\equiv C-Ph$	 **12**	78[g]
9[f]		$Br-C\equiv C-Ph$	 **13**	74[g]
10[f]		$Br-C\equiv C-Ph$	 **14**	60[g]

[a] Isolated yields of products purified by column chromatrography. [b] Reactions conducted using improved protocol with 1.15-1.5 equiv of alkynyl halide and 25 equiv of pyridine. [c] This work. [d] See ref. 11. [e] See ref. 5b. [f] Reaction conducted using original protocol with 1.5-2 equiv of alkynyl bromide. [g] See ref. 16.

For the synthesis of most ynamides, we have found both our method and the Hsung "second-generation" procedure to be reliable and reproducible on both small and large (i.e., multigram) scales. Recently, Tam and co-workers reported an alternative *N*-alkynylation protocol[24] that involves a melding of the procedures previously developed in our laboratory and that of Hsung. Tam's conditions involve the use of catalytic (8–40 mol%) CuI and 1,10-phenanthroline (12–46 mol%), with slow addition of 1.0–1.7 equiv of KHMDS over several hours to a hot (90 °C) solution of the copper salt, ligand, amine derivative, and alkynyl bromide in toluene. Tam was motivated to introduce this modified procedure when he encountered difficulties in reproducing results previously reported by both our group and that of Hsung. For example, Tam reports obtaining none of the desired ynamide from the reaction of 1-bromo-2-phenylacetylene with $BnNHCO_2Me$ using either our method or the method of Hsung. Hsung had previously reported obtaining this ynamide in 73% yield,[23] and we had reported the synthesis of the corresponding Boc derivative in 61% yield.[16]

We investigated the coupling of $BnNHCO_2Me$ with 1-bromo-2-phenylacetylene in some detail in an attempt to identify the experimental variables that might be responsible for Tam's inability to reproduce our results and the results of Hsung and co-workers.[11] We obtained the expected ynamide **11** in 63% yield using our method (Table 1, entry 7), and in 79% yield by employing the "second-generation" procedure of Hsung. In our experience, both methods have proved to be highly reproducible. We have noted, however, that results employing our method are affected by the quality of the pyridine used in the reaction. Thus, the yield reported here for ynamide **11** was obtained using pyridine freshly distilled from CaH_2 or KOH as recommended in our original report.[16] When pyridine (Alfa Aesar, 99%, 0.1% water content) from a freshly opened bottle was used (without distillation) instead, the yield of ynamide product declined to 52%. Most significantly, when distilled pyridine that had then been exposed to the atmosphere for several days was used for the *N*-alkynylation, none of the desired ynamide was formed.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139. Financial support by the National Institutes of Health (GM 28273) and Merck Research Laboratories is gratefully acknowledged. A.L.K was supported in part by a Massachusetts

Institute of Technology Leventhal Presidential Fellowship and by the American Council of Independent Laboratories.

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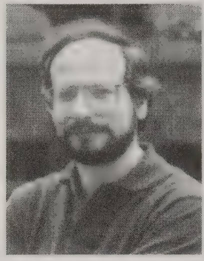
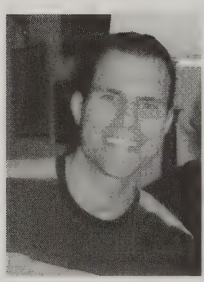
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Allylamine: 2-Propen-1-amine; (107-11-9)
Methyl chloroformate: Carbonochloridic acid, methyl ester; (79-22-1)
N-(Methoxycarbonyl)-2-propenylamine: Carbamic acid, 2-propenyl-, methyl ester; (19364-21-7)
1,3-Decadiyne; (55682-66-1)
N-Bromosuccinimide: 2,5-Pyrrolidinedione, 1-bromo-; (128-08-5)
Potassium hexamethyldisilazide: Silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-, potassium salt; (40949-94-8)
Copper(I) iodide; (7681-65-4)



Rick L. Danheiser received his undergraduate education at Columbia where he carried out research in the laboratory of Professor Gilbert Stork. He received his Ph.D. at Harvard in 1978 working under the direction of E. J. Corey on the total synthesis of gibberellic acid. Dr. Danheiser is the A. C. Cope Professor of Chemistry at MIT where his research focuses on the design and invention of new annulation and cycloaddition reactions, and their application in the total synthesis of biologically active compounds.

Amanda L. Kohnen was born in 1981 in West Hollywood and grew up in Yuma, Arizona. She did her undergraduate work at the University of California, San Diego and received a B.S. degree in Chemistry in 2004. She is now pursuing graduate studies at the Massachusetts Institute of Technology where her research under the direction of Professor Rick Danheiser involves the development of new synthetic methods and the total synthesis of biologically active natural products. Ms. Kohnen is the recipient of an MIT Leventhal Presidential Fellowship, a Pfizer Research Fellowship, and an NSF Graduate Research Fellowship.

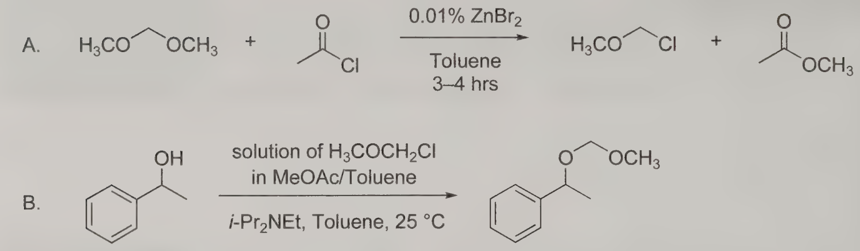


Joshua R. Dunetz received his Ph.D. from MIT in 2005 after completing graduate studies under the direction of Professor Rick L. Danheiser. His graduate research focused on the synthesis of ynamides and their cycloadditions with conjugated enynes in a strategy for the synthesis of indolines and indoles. In other graduate work, Dr. Dunetz studied the synthesis of nitrogen heterocycles in environmentally friendly reaction media such as supercritical carbon dioxide. He is currently a postdoctoral research associate with Professor William Roush at Scripps Florida working on the total synthesis of macrolide natural products.

Xiaorong Liu graduated with BS and MS degrees in Chemistry from Nanjing University in China where she carried out research on the synthesis of organic conducting polymers in the laboratory of Professor Xue Gi. In the fall of 1999, she began graduate studies under the direction of Professor Robert K. Boeckman, Jr. at the University of Rochester where her PhD thesis focused on the total synthesis of (–)-Apoptolidin. In the fall of 2004, she joined the laboratory of Professor Denmark as a postdoctoral associate at University of Illinois at Urbana-Champaign.

SYNTHESIS OF ALPHA-HALO ETHERS FROM SYMMETRIC ACETALS AND *in situ* METHOXYMETHYLATION OF AN ALCOHOL

[1-Methoxymethoxy-1-phenylethane]



Submitted by Martin Berliner[1] and Katherine Belecki.
Checked by William D. Paquette and Peter Wipf.[2]

1. Procedure

CAUTION: Chloromethyl methyl ether is an OSHA registered carcinogen and is listed as an extremely hazardous substance by the EPA and the European Community. Other α-halo ethers are likely to be carcinogenic. Exercise due caution to minimize handling of these compounds.

A. *Chloromethyl methyl ether as a solution in toluene.* A three-necked 500-mL flask is fitted with a magnetic stirbar, thermometer, reflux condenser with nitrogen inlet, and addition funnel (Note 1). The vessel is charged with dimethoxymethane (22.1 mL, 250 mmol, 1 equiv) (Note 2), toluene (66 mL, 3 volumes) (Notes 3, 4) and $ZnBr_2$ (5.6 mg, 0.01 mol%) (Notes 5, 6). The zinc bromide dissolves shortly after addition. Acetyl chloride (17.8 mL, 250 mmol, 1 equiv) (Note 7) is placed in the addition funnel and then introduced into the reaction mixture at a constant rate over 5–15 minutes (Note 8). The addition funnel is rinsed with a minimum volume of toluene (5 mL) directly into the reaction mixture. The reaction self-heats slowly to 40–45 °C and then cools to ambient temperature over 2–3 h, at which time the exchange reaction is typically complete (Note 9). This clear, colorless solution of chloromethyl methyl ether in toluene is employed directly in the subsequent step without further manipulation (Note 10).

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B. *1-Methoxymethyl-1-phenylethane.* The reaction flask containing a toluene solution of chloromethyl methyl ether (250 mmol, 1.5 equiv) prepared above is immersed in a cold water bath and the contents cooled to 5–10 °C. α-Phenethyl alcohol (20 mL, 166 mmol, 1 equiv) is charged to the addition funnel and added in one portion (Note 11). Diisopropylethylamine (36.0 mL, 208 mmol, 1.25 equiv) is charged to the addition funnel and added to the reaction mixture dropwise over 30 min (Notes 12, 13). The internal temperature of the mixture is maintained below 25 °C during and immediately after the amine addition, and once heat evolution has ceased, the reaction mixture is allowed to come to ambient temperature and then stirred for 12 h. At this time the starting material is consumed (Note 14). The orange solution is diluted with ethyl acetate (100 mL) and a saturated aqueous NH_4Cl solution (100 mL), and the biphasic mixture stirred vigorously for a minimum of five minutes to ensure all residual chloromethyl methyl ether is decomposed (Note 15). The layers are separated and the resulting clear, colorless organic layer is washed once with water (100 mL), once with brine (100 mL), dried with $MgSO_4$ and concentrated by rotary evaporation to a clear, colorless oil (Note 16). The material is transferred to a 50-mL round-bottomed flask equipped with a magnetic stirbar and a short-path distillation head. The product is purified by distillation, collecting a single fraction (bp 60–63 °C, 0.5 mmHg) of 1-methoxymethoxy-1-phenylethane as a clear, colorless oil (26.2 g, 157 mmol, 95% yield) (Notes 17, 18, 19).

2. Notes

1. The success of the reaction does not depend on having previously dried the glassware.

2. Dimethoxymethane was obtained from Acros Organics at 99.5+% purity and used as received. The submitters used dimethoxymethane, obtained from Aldrich Chemical Co. at 99% purity, as received.

3. ACS grade toluene was employed without additional purification. A similar grade of dichloromethane, dichloroethane and alkyl acetate esters (i.e. ethyl acetate, isopropyl acetate) can be substituted for toluene with no change in reaction behavior or yield.

4. Although the reaction can be conducted neat, the authors strongly recommend using a co-solvent to mitigate the strongly exothermic nature of the process. The volume of solvent employed in this reaction was chosen to

provide a good balance of reaction rate and thermal control. If less solvent is employed, active cooling should be utilized to keep the reaction temperature below 45 °C.

5. Zinc bromide (anhydrous powder, 98+%) was obtained from Acros Organics and used as received.

6. For small- and medium-scale reactions with dimethoxymethane, such small amounts of catalyst are required that the authors found it easiest to dispense the correct amount of catalyst from standard solutions of $ZnBr_2$ in dimethoxymethane (20–50 mg/mL).

7. The submitters obtained acetyl chloride from Aldrich Chemical Co. and Acros Organics at 97–99% purity and used it as received.

8. The reaction temperature increases slightly upon addition of acetyl chloride; the reaction is not dose controlled at this temperature. For a dose-controlled addition, the submitters recommend pre-heating the solvent/acetal/catalyst solution to 40 °C before dropwise addition of the halogenating agent, since the catalyzed exchange reaction is very rapid once the temperature exceeds 40 °C.

9. A small amount of the reaction mixture (20 mL) is dissolved in 0.6 mL of $CDCl_3$ for the analysis. The ratio of AcCl (δ 2.6 ppm):MeOAc (δ 2.0 ppm) is utilized to evaluate reaction progress as a small excess of dimethoxymethane is usually present once the exchange is complete (typical ratio MeOAc:AcCl $\geq$ 99:1). ^{1}H NMR ($CDCl_3$) δ: 5.44 (s, 2 H, MOMCl), 3.64 (s, 3 H, MeOAc), 3.49 (s, 3 H, MOMCl), 2.03 (s, 3 H, MeOAc). *In situ* IR can also be employed to monitor reaction progress without requiring sampling of the reaction contents.

10. The solution of MOMCl in toluene, prepared using this stoichiometry and solvent volume, has a concentration of approx 3.5 M. According to the submitters, concentrations of MOMCl in toluene at approx 2.1 M (18% w/w) have a density of 0.91 g/mL and are stable for months if adequately sealed.

11. No heat evolution is observed during the addition.

12. Addition of the amine base results in a strong and extended exotherm as the reaction proceeds. In the absence of external cooling the reaction temperature can exceed 60 °C.

13. The order of addition of the amine and alcohol can be interchanged without affecting the purity or yield of the product. The following procedure is suggested: The solution of MOMCl is cooled to 10 °C and the base is added, slowly at first, keeping the internal temperature below 25 °C. Alcohol

is added in one portion and the solution allowed to warm to ambient temperature and stirred until complete. Workup is as described in the main procedure.

14. Analysis is by HPLC. Starting material t_R 4.46 min, product t_R 7.25 min. Agilent Zorbax® SB-C8 column 4.6 x 150 mm, 2 mL/min flow, using acetonitrile and 0.1% $HClO_4/H_2O$ as the eluent. The following gradient profile is used: 2 min isocratic (10:90, organic:aqueous), ramp to 90:10 (organic:aqueous) over 6 min, then 2 min isocratic at 90:10 (organic:aqueous). Analysis can also be done by TLC (5:1, hexanes:EtOAc; α-phenethyl alcohol, R_f= 0.13; 1-methoxy-1-phenylethane, R_f= 0.5).

15. The quench is mildly exothermic as residual MOMCl decomposes. Typically all remaining α-chloro ether has been quenched five minutes after addition of the aqueous solution. Water and saturated carbonate solutions are also effective for quenching the reaction.

16. Typical mass of crude product is 27 g (98% yield) with purity >95%.

17. The submitters observed yields from 77–80%. Some decomposition of the product occurs during extended batch distillation, resulting in decreased yields. This is not observed when the purification is conducted on small scale in a Kugelrohr apparatus, or when a chromatographic purification is employed.

18. The checkers obtained a yield of 90% (12.5 g) on half-scale.

19. Physical data for the product: R_f 0.5 (5:1, hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.49 (d, J = 6.6 Hz, 3 H), 3.39 (s, 3 H), 4.55 (d, J = 6.9 Hz, 1 H), 4.59 (d, J = 6.6 Hz, 1 H), 4.76 (q, J = 6.6 Hz, 1 H), 7.27–7.37 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 55.3, 73.7, 94.0, 126.3, 127.5, 128.4, 143.2. IR (neat, cm^{-1}): 2976, 2931, 2887, 1451, 1155, 1099, 1036, 919, 759, 700. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.64.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Chloromethyl methyl ether (MOMCl) and other α-halo ethers are versatile reagents for protecting a variety of functional groups[3] and as precursors of carbenes, electrophiles and α-stannyl ethers that have wide use in organic synthesis.[4] This procedure describes an improved method for the generation of α-halo ethers from symmetric aliphatic acetals, including MOMCl and higher substituted analogs.[5] The original preparation of MOMCl in this series[6] and current commercial preparations utilize the reaction between methanol, formaldehyde and hydrogen chloride and produce substantial amounts of the very highly carcinogenic bis(chloromethyl) ether which cannot be readily separated by distillation. More recent procedures[7] have employed the exchange reaction between dimethoxymethane and a halide donor catalyzed by protic acid; these minimize formation of bis(chloromethyl)ether and are preferred to the original preparation. These methods employ different halide sources and different acid catalysts, but all require extended (2–24 hours or more) reflux to effect full exchange, and due to the high vapor pressure of the reactants and products, efficient condensers are required to minimize material loss.

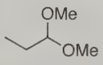
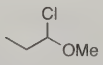
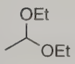
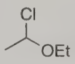
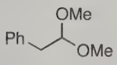
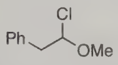
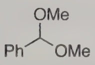
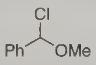
The present method utilizes catalytic zinc(II) salts (0.001 to 0.01 mol%) to accelerate the exchange reaction between halide donors and acetals. Reactions typically are complete in one to four hours irrespective of the scale of the preparation (mmol through mole scale) without the need for external heating. A range of zinc(II) salts can be utilized, with $Zn(OTf)_2$, $ZnBr_2$ and $Zn(OAc)_2$ being the easiest to manipulate. Acid halides and thionyl chloride (but not thionyl bromide) are effective as the halide source (Table 1). A variety of symmetric aliphatic acetals participate in the reaction to give synthetically useful α-halo ethers (Table 2). The solutions of α-halo ethers are employed without isolation in base-mediated reactions where the presence of the ester by-product does not interfere, including alkylations of acids, alcohols, phenols and stabilized enolates under the usual conditions (Table 3). Since α-halo ethers are hazardous (some are carcinogenic; others are possible carcinogens), this procedure illustrates a convenient on-demand synthesis and use of these reagents without isolation or unnecessary handling. The improved safety of this telescoped procedure addresses concerns of both academic and industrial chemists who are under increasing pressure to reduce laboratory hazards.

Table 1. Halogen Sources

$$(MeO)_2CH_2 + X{-}R \xrightarrow[25\ ^\circ C]{0.01\%\ ZnBr_2} MeOCH_2X + MeOR$$

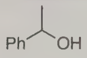
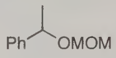
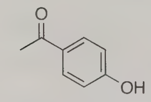
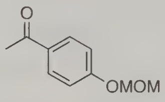
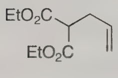
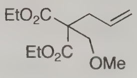
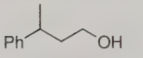
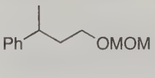
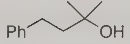
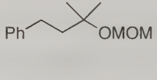
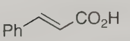
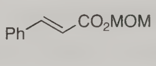
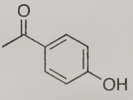
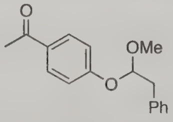
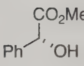
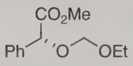
Entry	Halide Source	Equiv required	Time
1	$(COCl)_2$	0.5	< 5 min
2	RCOCl	1.0	30 min
3	$SOCl_2$	0.5	30 min
4	CH_3COBr	1.0	45 min

Table 2. Acetals Employed in the Exchange Reaction

Entry	Acetal	α-Halo Ether	Halide Source	Catalyst	Time[a]
1	$(EtO)_2CH_2$	$EtOCH_2Cl$	AcCl	$ZnBr_2$	4 hr
2			$(COCl)_2$	$Zn(OTf)_2$	1 hr
3			AcCl	$ZnBr_2$	1 hr
4			AcCl	$Zn(OTf)_2$	30 min
5			AcCl	$Zn(OTf)_2$	30 min

(*a*) Time to completion of exchange reaction by NMR spectroscopy.

Table 3: Alkylation Reactions of In Situ Generated α-Halo Ethers[a]

Entry	Starting Material	Product	Yield[b] (%)
1			92
2			86
3[c]			80
4			92
5			92
6	$PhCO_2H$	$PhCO_2MOM$	92
7			96
8			93
9			85

(*a*) Reactions are conducted on 10-20 mmol scale with 1.5–2.0 equivalents of α-halo ether and 1.25 equivalents of *i*-Pr_2NEt in toluene for 12–16 hours followed by a standard aqueous workup as described in this procedure. (*b*) Yield of purified product. (*c*) Malonate anion was prepared using NaH in THF followed by addition to a MOMCl solution prepared in toluene.

1. Chemical Research and Development, Pfizer Global Research and Development, Groton, CT 06340.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
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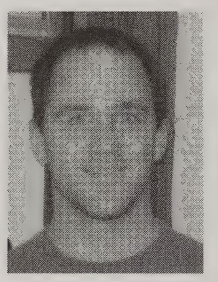
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dimethoxymethane; (109-87-5)
Zinc bromide; (7699-45-8)
Acetyl chloride; (75-36-5)
Chloromethyl methyl ether: Methane, chloromethoxy-; (107-30-2)
α-Phenethyl alcohol: Benzenemethanol, α-methyl-; (98-85-1)
Diisopropylethylamine: 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)-: (7087-68-5)
1-Methoxymethoxy-1-phenylethane: Benzene, [1-(methoxymethoxy)ethyl]-; (94073-86-6)

Marty Berliner was born in Denver, Colorado in 1968. He received a B.S. in Physics from Harvey Mudd College in 1990 and then switched fields to organic chemistry in graduate school, where he earned a Ph.D. with Tarek Sammakia (University of Colorado, Boulder) developing the asymmetric Diels-Alder reaction of oxocarbenium ions (1996). Following postdoctoral research with David Williams at Indiana University, he joined Pfizer in 1999 and is currently a senior principal scientist in the early candidate group in Chemical Research and Development.

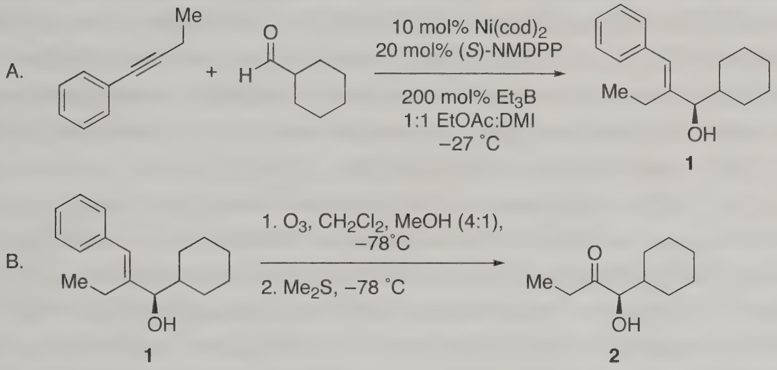
Katherine Belecki was born in Silver Spring, Maryland, in 1979. After completing her B.A. in Chemistry at Williams College in 2001, she spent two years working with Dr. Marty Berliner in the early development and discovery support group at Pfizer. She is currently pursuing a doctorate degree in the lab of Dr. Craig Townsend at the Johns Hopkins University in Baltimore, investigating biosynthetic pathways of polyketide natural products.



William D. Paquette received his B.S. degree at the University of New Hampshire in 2000 and performed research under Prof. Charles Zercher. He then obtained his Ph.D. in 2006 from the University of Notre Dame with Prof. Richard E. Taylor. His graduate research focused on studies toward the total synthesis of 20-deoxyapoptolidin. At Notre Dame, he developed unique methodology to construct contiguous *(E)*-trisubstituted olefins utilizing a thionyl chloride-induced rearrangement. Currently, he is conducting postdoctoral research under the supervision of Prof. Peter Wipf at the University of Pittsburgh on the synthesis of novel phosphatase inhibitors as well as the natural product wortmannin.

(*S*)-(+)-NEOMENTHYLDIPHENYLPHOSPHINE IN NICKEL-CATALYZED ASYMMETRIC REDUCTIVE COUPLING OF ALKYNES AND ALDEHYDES: ENANTIOSELECTIVE SYNTHESIS OF ALLYLIC ALCOHOLS AND α-HYDROXY KETONES

[(*R*)-Butan-2-one, 1-cyclohexyl, 1-hydroxy-]



Submitted by Aaron R. Van Dyke, Karen M. Miller, and Timothy F. Jamison.[1]
Checked by Matthew J. Fleming and Mark Lautens.

1. Procedure

A. *(R)-(E)-2-Benzylidiene-1-cyclohexyl-butan-1-ol.* In a glovebox, a flame-dried 500-mL round-bottomed flask is charged with Ni(cod)$_2$ (1.38 g, 5.00 mmol) (Note 1) and (*S*)-(+)-neomenthyldiphenylphosphine (3.24 g, 10.0 mmol) (Note 2). The flask is sealed with a septum, removed from the glovebox, and transferred to a fume-hood. An argon inlet (Note 3) is then attached to the flask and degassed EtOAc (50 mL) (Note 4), freshly distilled, degassed DMI (50 mL) (Note 5), and triethylborane (14.5 mL, 100 mmol) (Note 6) are added sequentially via syringe. *Caution! Triethylborane is extremely pyrophoric.* The solution is allowed to stir 15 min at room temperature and then placed in a –27 °C bath (Note 7) for 30 min. 1-Phenyl-1-butyne (7.1 mL, 50 mmol) (Note 8) is added in one portion via syringe followed by addition of cyclohexanecarboxaldehyde (9.1 mL, 75 mmol)

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(Note 9) via syringe pump over 9 h to the solution in a –27 °C bath. The reaction is stirred at –27 °C for 36 h, then quenched with saturated NH_4Cl (100 mL) (Note 10), 1M HCl (40 mL) at –27 °C. The solution is allowed to warm to room temperature and then stirred 15 min at room temperature. Air is vigorously bubbled through the reaction using a pasteur pipet for 30 min, which results in a light yellow emulsion (Note 11). The mixture is extracted with EtOAc (2 x 200 mL). The combined organic layers are washed twice with saturated NH_4Cl (300 mL), once with brine (300 mL) (Note 12), dried over $MgSO_4$ (10 g) (Note 13), filtered and concentrated on a rotary evaporator (20 °C, 11 mmHg, then 3 mmHg) to remove trace EtOAc. The resulting yellow oil is purified by flash chromatography on silica gel with a hexanes to 9:1 hexanes: ethyl acetate gradient (Note 14) to yield 10.87 g (89%) of **1** as a colorless oil (Note 15).

B. *(R)-1-Cyclohexyl-1-hydroxy-butan-2-one.* In a 1-L round-bottomed, one-necked flask with a magnetic stirbar, **1** (10.87 g, 44.5 mmol) is dissolved in methanol (60 mL) (Note 16) and dichloromethane (240 mL) (Note 17). The vessel is cooled to –78 ° C and ozone is bubbled through the solution suing a Pasteur pipet until a persistent blue color appears (approximately two hours) (Note 18). Argon is then bubbled through the solution for 30 min and dimethylsulfide (131 mL, 1780 mmol) is added (Note 19). The reaction is warmed slowly to ambient temperature and stirred for 13 h. The solvent and excess dimethylsulfide are removed by rotary evaporation (20 °C, 11 mmHg). The crude oil is purified by flash chromatography on silica gel, eluting with 50:1 hexanes: ethyl acetate (Note 20) to yield 5.30 g (70%) of **2** as a colorless oil (Note 21).

2. Notes

1. $Ni(cod)_2$ (98%) was purchased from Strem and used as received. The crystals should appear yellow in color, approximately 1.5 mm in diameter. $Ni(cod)_2$ appearing as a yellow powder or black should not be used. $Ni(cod)_2$ from other vendors should not be used. Silver colored deposits on the inside of $Ni(cod)_2$ vials were indicative of formation of Nickel mirror and other undesired species. Such samples should not be used.

2. (*S*)-(+)-Neomenthyldiphenylphosphine was purchased from Strem and used as received. NMDPP is moderately air sensitive and will oxidize unless opened, manipulated, and stored in a glovebox.

3. All "argon inlet" references are defined as inserting a 16-gauge needle attached to a positive flow of argon through the top of a rubber septum that is sealed around the flask neck with electrical tape.

4. Ethyl acetate (99.9%) was purchased from Burdick and Jackson, distilled over $MgSO_4$ (77 °C) and degassed by bubbling argon through it for 20 min. The checkers used ethyl acetate (99.5%) purchased from EMP Chemicals, Inc.

5. Dimethylimidizolidinone (99.5%) was purchased from Fluka, freshly distilled from CaH_2 (98 °C, 11.7 mmHg) prior to use. DMI is **extremely hygroscopic**, and trace water led to alkylative coupling (transfer of an ethyl group from Et_3B) instead of reductive coupling. Alkylative coupling was inseparable from the product by chromatography but identified by its carbinol proton ^1H NMR (400 MHz, $CDCl_3$) δ: 4.35 (d, $J = 9$, 1 H). Failure to use freshly distilled DMI gave approximately 10% alkylative coupling, whereas freshly distilled DMI gave 2% or less.

6. Triethylborane (98%) was purchased from Aldrich and used as received. The headspace of the Et_3B canister must be thoroughly purged with argon before opening. Triethylborane (Et_3B) in the syringe should be kept under argon at all times. Any Et_3B remaining in the syringe should be diluted with CH_2Cl_2 and quenched by stirring the solution open to air overnight in a hood. If a spark is observed at the needle tip, fresh Et_3B must be used. The checkers used triethylborane (98%) purchased from Strem.

7. Isopropyl alcohol bath temperature -27 ± 2 °C was maintained by Neslab Cryocool CC-60IIA. Temperature control was critical for maximum ee and yield. Due to the air sensitive nature of the reaction, internal temperature readings were not taken. All readings indicate the isopropanol bath temperature. The checkers used a Neslab Cryobath CB-80.

8. 1-Phenyl-1-propyne (99%) was purchased from Aldrich Chemical Co. and distilled from $MgSO_4$ (74 °C, 4 mmHg).

9. Cyclohexanecarboxaldehyde (98%) was purchased from Aldrich Chemical Co. and distilled from $MgSO_4$ (65 °C, 28 mmHg).

10. Ammonium chloride (reagent grade) was purchased from J.T. Baker and added to distilled tap water until saturated.

11. Air was vigorously bubbled through the quenched reaction to oxidize all nickel species to Ni(II) salts and to facilitate cleavage of the RO-BEt_2 bond, liberating the alcohol. An alternative to the NH_4Cl/HCl quench involved slow addition of a basic hydrogen peroxide solution via syringe (50 mL 30% H_2O_2 (Aldrich) in 200 mL 0.75M NaOH (Aldrich)). An 18-gauge

needle was inserted into the septum with this workup to avoid pressure buildup.

12. Sodium chloride (reagent grade) was purchased from Aldrich Chemical Co. and added to distilled tap water until saturated.

13. Magnesium sulfate (reagent grade) was purchased from Aldrich Chemical Co and used as received.

14. A column (10 cm by 22 cm) was prepared from a slurry of 600 g of silica gel (40 – 63μm, obtained from Silicycle) in hexanes. The oil was loaded onto this column and eluted with 2 L of hexanes, 2 L 95:5 hexanes : EtOAc, then 9:1 hexanes : EtOAc (approximately 3 L). Two silica gel columns were required for optimal purity.

15. The reaction was monitored by TLC. The product was visualized with UV followed by phosphomolybdic acid (10 g phosphomolybdic acid in 100 mL EtOH) stain, $R_f = 0.20$ (5:1, hexanes : EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99–1.30 (m, 8 H) 1.55–1.82 (m, 6 H), 2.00 (d, $J = 12.5$ Hz, 1 H), 2.21 (dq, $J = 19, 7.5$ Hz, 1 H), 2.36 (dq, $J = 19, 7.5$ Hz, 1 H), 3.93 (d, $J = 7$ Hz, 1 H), 6.45 (s, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 21.4, 26.1, 26.3, 26.5, 28.3, 30.1, 41.6, 81.4, 126.3, 126.4, 128.1, 128.6, 137.6, 145.5; IR (thin film NaCl): 3395, 3055, 3023, 2927, 2851, 1599, 1493, 1448, 1308, 1261, 1173. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.30; H, 9.81. Enantiomeric excess (87%) was established by chiral HPLC (Chiralcel OD, hexanes: 2-propanol, 98:2, 1 mL/min): t_R[(R)-**1**] = 14.5 min, t_R[(S)-**1**] = 16.5 min. Repeating the reaction on a half-scale gave 90% yield and 88% ee.

16. Methanol (99.9%) was purchased from VWR and used as received. The checkers used methanol (99.8%) purchased from Caledon, Inc.

17. Dichloromethane (HPLC grade) was purchased from Burdick and Jackson and used as received. The checkers used dichloromethane (99.5%) purchased from Caledon, Inc.

18. Clear Water Tech Ozone generator, model CD1500.

19. Dimethylsulfide (99+%) was purchased from Aldrich Chemical Co. and used as received. With the exception of rotary evaporation, all manipulations involving dimethylsulfide and dimethylsulfide-containing solutions were performed in a well-ventilated fume hood. The distillate collected during rotary evaporation was treated with 1:1 solution of commercial-grade (Clorox®) and water (2 x 200 mL) prior to disposal. All reaction glassware and the collection bulb on the rotary evaporator were washed with a bleach solution (1:1, bleach:water) after use.

20. A column (6.5 cm by 12 cm) was prepared from 225 g of silica gel (40 – 63μm, obtained from Silicycle).

21. Product was visualized with PMA stain, $R_f = 0.25$ (8:2, hexanes: ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13–1.35 (m, 8 H), 1.48 (dq, $J = 12.5, 4$ Hz, 1 H), 1.64–1.83 (m, 5 H), 2.41–2.57 (overlapping dq, $J = 19, 7.5$ Hz, 2 H), 3.41 (d, $J = 10$ Hz, 1 H), 4.06 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.6, 25.1, 25.8, 26.0, 26.5, 30.1, 31.4, 41.4, 80.5, 213.0; IR (thin film NaCl): 3474, 2976, 2931, 2853, 1709, 1450, 1406, 1349, 1260, 1105; Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.35; H, 10.55. Enantiomeric excess 88%, established by chiral GC (Alltech B-PH, column = 95 °C, injector = 200 °C, flow (H_2) = 2 mL/min): t_R[(R)-**2**] = 30.7 min, t_R[(S)-**2**] = 31.5 min. The checkers could not get separation of peaks on Alltech B-PH column (10 years old) using the submitter's conditions. Changing the column temp to 80 °C gave two peaks, but without baseline separation. Enantiomeric excess could be estimated to be between 85–90%: t_R[(R)-**2**] = 70.6 min, t_R[(S)-**2**] = 74.2 min. Repeating the reaction on a half-scale gave 66% yield and 85–90% ee.

Safety and Waste Disposal Information

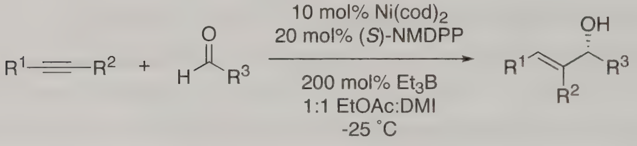
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Allylic alcohols are synthetically useful intermediates and are present in a variety of natural products. An established method for accessing these compounds involves the addition of alkenyl halides (Nozaki-Hiyama-Kishi reaction[2]) or alkenyl metals (prepared via hydroboration[3] or hydrozirconation[4] of alkynes) to aldehydes. All of these involve the use of a stoichiometric amount of transition metal. Intramolecular[5] and intermolecular[6] nickel-catalyzed reductive coupling of alkynes and aldehydes have been reported in the literature, and that described here is the only one that affords products with high levels of enantioselectivity.[7]

The nickel-catalyzed asymmetric reductive coupling of alkynes and aldehydes reported herein allows rapid access to enantiomerically enriched (*E*)-trisubstituted allylic alcohols.[8] The catalyst is derived from $Ni(cod)_2$ and

Table 1. Asymmetric catalytic reductive coupling of alkynes and aldehydes.[a]



entry	R^1	R^2	R^3	yield (%),[b] regioselectivity[c]	ee (%)[d]
1	Ph	Me	*i*–Pr	95 (>95:5)	90[e]
2	"	"	Cy	97 (>95:5)	90
3	"	"	Ph	79 (91:9)	73
4	"	"	*n*–Pr	82 (>95:5)	65
5	(*p*-MeO)Ph	"	*i*–Pr	80 (>95:5)	88
6	(*p*-Cl)Ph	"	"	75 (>95:5)	83
7	(*p*-CF_3)Ph	"	"	78 (>95:5)	81
8	(*o*-Me)Ph	"	"	86 (>95:5)	84
9	1-naphthyl	"	"	93 (>95:5)	90
10	Ph	Et	"	81 (>95:5)	93
11[f]	Ph	Et	Cy	78 (>95:5)	89
12	"	*n*–Pr	*i*–Pr	74 (>95:5)	92
13	"	*i*–Pr	"	58[g] (>95:5)	92
14	"	cyclopropyl	"	67 (>95:5)	92
15	"	CH_2OTBS	"	59 (>95:5)	85
16	"	CH_2NHBoc	"	60 (>95:5)	96
17	"	$SiMe_3$	*n*–Pr	43[g] (>95:5)	92
18	*n*–Pr	*n*–Pr	*i*–Pr	35[g] (–)	42
19	Ph	H	"	15 (>95:5)	75

[a] Experimental procedure: A solution of $Ni(cod)_2$ (0.05 mmol), (*S*)-(+)-NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to –25 °C. The alkyne (0.50 mmol) was added, and then the aldehyde (1.0 mmol) was added dropwise via syringe over 8 h. After 36 h, saturated aqueous NH_4Cl (2 mL) and 1 M HCl (0.5 mL) were added and the mixture was extracted with EtOAc (3 x 10 mL). Crude material was purified by silica gel chromatography. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC or GC analysis. [e] Absolute configuration determined to be (*R*) by Mosher's ester analysis. [f] Performed on 5.0 mmol scale. [g] Some alkylative coupling (transfer of Et from Et_3B instead of H) was observed.

(*S*)-(+)-neomenthyldiphenylphosphine (NMDPP), a commercially available phosphine, and the terminal reductant is Et_3B. The enantioselective, catalytic reductive coupling exhibits excellent regioselectivity (>95:5) and exclusive *cis* addition across the alkyne. Ozonolysis yields an α-hydroxyketone with complete preservation of enantiomeric purity. In addition to being an example of a useful family of building blocks, the TBS ether of **2** was developed by Masamune for use in asymmetric aldol reactions.[9]

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139. e-mail: tfj@mit.edu.
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Ni(cod)$_2$: Nickel, bis[(1,2,5,6-η)-1,5-cyclooctadiene]-; (1295-35-8)

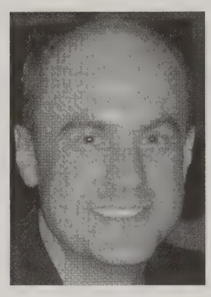
(*S*)-(+)-Neomenthyldiphenylphosphine: Phosphine, [(1*S*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]diphenyl-; (43077-29-8)

Triethylborane; (97-94-9)

Dimethylimidizolidinone (DMI): 1,3-Dimethyl-2-imidazolidinone; (80-73-9)

1-Phenyl-1-butyne: 1-Butynylbenzene; (622-76-4)

(*R*)-(*E*)-2-benzylidiene-1-cyclohexyl-butan-1-ol: Cyclohexanemethanol, α-[(1*E*)-1-(phenylmethylene)propyl]-, (α*R*)-; (512785-86-3)
(*R*)-Butan-2-one, 1-cyclohexyl, 1-hydroxy-; (512785-95-4)
Dimethylsulfide: Methane, thiobis-; (75-18-3)



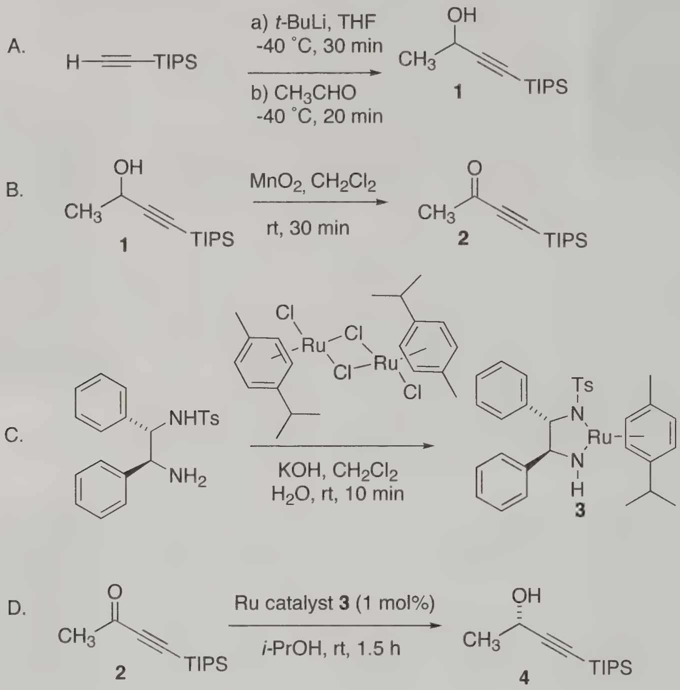
Tim Jamison received his undergraduate education at the University of California, Berkeley, where he conducted undergraduate research under the direction of Prof. Henry Rapoport. A Fulbright Scholarship supported ten months of research in Prof. Steven A. Benner's laboratories at the ETH, and thereafter he undertook his PhD studies at Harvard University with Prof. Stuart L. Schreiber. He then moved to the laboratory of Prof. Eric N. Jacobsen at Harvard University, where he was a Damon Runyon-Walter Winchell postdoctoral fellow. In 1999, he began his independent career at MIT, where his research program focuses on the development of new synthetic methods and their implementation in the total synthesis of natural products.

Aaron Van Dyke was born and raised in Yakima, WA. A Sullivan Scholarship supported four years of study at Seattle University, the last two of which were spent conducting undergraduate research with Prof. Greg T. Spyridis. Upon earning a B.S. in chemistry in 2004, he moved to the laboratory of Prof. Timothy F. Jamison at the Massachusetts Institute of Technology for doctoral studies. His current research focuses on the development of methods for the synthesis of functionalized cyclic ethers, a motif common to the ladder polyether class of marine natural products.

Karen Miller grew up in Lyndonville, VT, and received her undergraduate education at Dartmouth College in Hanover, NH. While at Dartmouth she performed undergraduate research with Professors Gordon W. Gribble and David M. Lemal, and also completed a summer internship in the Chemical and Screening Sciences Department at Wyeth Research in Pearl River, NY. She conducted her doctoral studies at MIT in the laboratory of Prof. Timothy F. Jamison, where she focused on the development of nickel-catalyzed, carbon-carbon bond-forming reactions. In 2005, she joined the Global Discovery Chemistry/Oncology department at Novartis Institutes for Biomedical Research in Cambridge, MA.

Matthew Fleming was born in 1978 in London, UK. After obtaining his MSci in Chemistry (1st class honors) in 2002 from King's College London, he moved to the University of Oxford (Hertford College) and in 2005 completed his PhD under the supervision of David M. Hodgson. His research was sponsored by GlaxoSmithKline and was concerned with the development of new reaction methodology involving metalated heterocycles and sulfur ylides. He is currently a postdoctoral research assistant with Prof. Mark Lautens at the University of Toronto, working in the area of natural product synthesis.

SYNTHESIS OF 4-TRIISOPROPYLSILYL-3-BUTYN-2-OL BY ASYMMETRIC TRANSFER HYDROGENATION



Submitted by James A. Marshall, Patrick Eidam, and Hilary Schenck Eidam.[1a]

Checked by Kai Zhang and Dennis P. Curran.[1b]

1. Procedure

A. *(rac)-4-Triisopropylsilyl-3-butyn-2-ol (1).* A single-necked, flame-dried, 250-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon and charged with triisopropylsilyl acetylene (95%, 6.1 mL, 4.75 g, 26.0 mmol) (Note 1) and dry THF (54 mL) (Note 2) by syringe through the septum. The reaction mixture is cooled to –40 °C (bath temperature) by means of a dry ice-acetonitrile bath and *tert*-BuLi (1.7 M in pentane, 18 mL, 32.3 mmol) is added dropwise by means of a syringe (Note 3). The resulting bright yellow mixture is stirred at –40 °C for 30 min and then ACS reagent grade

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acetaldehyde (>99.5%, 2.3 mL, 39.2 mmol) is added in one portion by means of a syringe. The reaction mixture is stirred for 20 min at –40 °C and then poured over a rapidly stirring solution of saturated aqueous NH_4Cl (75 mL) at room temperature. After 15 min, the phases are separated and the aqueous layer is extracted with diethyl ether (2 x 40 mL). The combined organic extracts are washed with brine, dried over $MgSO_4$, filtered, and the solvent is removed with a rotary evaporator (40 °C, water aspirator pressure). The residue is purified by bulb-to-bulb distillation (95 °C, 0.2 mmHg; Note 4) to yield the racemic alcohol (5.8 g, 98%) as a clear oil (Notes 5, 6, 7). This material is used in the next step without further purification.

B. 4-Triisopropylsilyl-3-butyn-2-one (2). A one-necked, flame-dried, 250-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. The septum is temporarily removed and the flask is charged sequentially with CH_2Cl_2 (54 mL), 4-triisopropylsilyl-3-butyn-2-ol (**1**) (5.8 g, 25.6 mmol) and technical grade MnO_2 (85%, 34.4 g, 336.9 mmol) (Notes 8, 9), which is added in one portion. The reaction mixture is stirred at room temperature for 30 min and then filtered through a short pad of Celite. The Celite is washed with CH_2Cl_2 (2 x 30 mL) and the solvent is removed on a rotary evaporator (40 °C, water aspirator pressure). The resulting yellow oil is purified by bulb-to-bulb distillation (80 °C, 0.2 mmHg; Note 4) to yield ketone **2** (5.0–5.1 g, 87–89%) as a clear oil (Notes 10, 11). This material is used in the next step without further purification.

C. *RuCl[(S,S)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) (3).* (Note 12). A one-necked, flame-dried, 50-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. The septum is temporarily removed and the flask is charged with CH_2Cl_2 (6 mL), (1*S*,2*S*)-(+)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylene-diamine (126 mg, 0.34 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (107 mg, 0.17 mmol), and powdered KOH (141 mg, 2.5 mmol) (Note 1). The resulting orange mixture is stirred for 5 min at room temperature and then distilled H_2O (6 mL) is added in one portion by means of a syringe. The resulting biphasic mixture is stirred for 10 min during which time the organic phase turns dark purple. The mixture is transferred to a separatory funnel, diluted with 10 mL of H_2O and the layers are separated. The aqueous phase is extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts are dried over CaH_2 (Note 1), filtered and solvent is removed with a rotary evaporator (40 °C, water aspirator pressure) to furnish the catalyst **3** (180–182 mg, 86–87%) as a dark purple solid that is used in the subsequent reduction without additional purification.

D. *(S)-4-Triisopropylsilyl-3-butyn-2-ol (4)*. A one-necked, flame-dried, 500-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. Isopropyl alcohol (250 mL) and 4-triisopropylsilyl-3-butyn-2-one (**2**) (5.1 g, 22.7 mmol) are added to the flask through the septum by syringe. The ruthenium catalyst **3** (180 mg, 0.3 mmol) is taken up in a minimal amount of CH_2Cl_2 (~5 mL) and added to the reaction mixture in one portion by means of a syringe. The mixture is stirred for 1.5 h and then the solvent is removed with a rotary evaporator (40 °C, water aspirator pressure). The brown residue is purified by bulb-to-bulb distillation (95 °C, 0.2 mmHg; Note 4) to yield the alcohol **4** (5.0 g, 85% for three steps) as a clear oil (Notes 13, 14, 15).

2. Notes

1. All chemicals were purchased from Aldrich Chemical Co. and were used without further purification. The submitters purchased THF and CH_2Cl_2 as optidry Fischer Paks from Fischer Scientific. The checkers purchased dry CH_2Cl_2 from Aldrich and used THF from a sodium/benzophenone still.

2. The submitters reported that the use of diethyl ether in place of THF resulted in diminished yields and the formation of impurities not separable by distillation.

3. The submitters reported that the use of *n*-BuLi (20.2 mL of 1.6 M *n*-BuLi in hexanes) afforded the adduct **1** in quantitative yield. The spectra of the sample prepared in this way were identical to those of the sample from the *tert*-BuLi experiment.

4. Bulb-to-bulb distillations were performed with an Aldrich Kugelrohr apparatus.

5. Physical characteristics for 4-triisopropylsilyl-3-butyn-2-ol **(1)**: R_f = 0.41 (15% EtOAc-hexane) on Merck silica gel 60 F 254 precoated 250 μm plates; IR (film): 3325, 2943, 2866, 2173, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (m, 21 H), 1.48 (d, J = 6.6 Hz, 3 H), 1.78 (s, 1 H), 4.55 (q, J = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.1, 18.5, 24.5, 58.7, 84.3, 109.8.

6. The submitters reported that the product was contaminated by up to

3% triisopropylacetylene in some runs. This was analyzed by integration of the alkynyl H signal at 2.35 ppm in the ^{1}H NMR spectrum.

7. An analytical sample was prepared by chromatography on silica gel. A 1.5 cm x 20 cm glass column packed with 9 g of EMD silica gel 60 was used to purify 20 mg of alcohol by elution with 10% diethyl ether in hexanes. Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.96; H, 11.66.

8. MnO_2 was purchased from Aldrich Chemicals and dried in an oven at 110 °C overnight prior to use.

9. The submitters reported that exposure to less than 13 equiv of MnO_2 resulted in incomplete conversion and formation of byproducts upon prolonged reaction times.

10. Physical characteristics for 4-triisopropylsilyl-3-butyn-2-one **(2)**: R_f = 0.76 (15% EtOAc-hexane) on Merck silica gel 60 F 254 precoated 250 µm plates; IR (film): 2946, 2868, 2147, 1684, 1464, 1196 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.10 (m, 21 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3, 18.4, 32.8, 95.2, 104.6, 184.4.

11. An analytical sample was prepared by chromatography on silica gel. (A 1.5 cm x 20 cm glass column packed with 9 g of of EMD silica gel 60 was used to purify 20 mg of ketone by elution with 5% diethyl ether in hexanes. Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.56; H. 10.89.

12. The procedure described for the preparation of RuCl[(*S*,*S*)-$NTsCH(C_6H_5)CH(C_6H_5)NH_2(\eta^6$-cymene) was taken from reference 9.

13. Physical characteristics for *(S)*-4-triisopropylsilyl-3-butyn-2-ol (**4**): Same as for racemic 4-triisopropylsilyl-3-butyn-2-ol; $[\alpha]_D^{20}$ –21.3 (c = 1.58, $CHCl_3$). The er of this material was found to be >95:5 by ^{19}F NMR analysis [δ–73.68 ppm (major) and –73.02 ppm (minor), in $CDCl_3$ versus benzotrifluoride as an internal standard at –63.72 ppm] of the *(R)*-Mosher ester. To prepare the Mosher ester, 4-triisopropylsilyl-3-butyn-2-ol (4 mg), (*S*)-(+)-methoxy-α-trifluoromethylphenylacetyl chloride (5 µL) and dry pyridine (0.15 mL) were added to a one-necked, flame-dried, 5-mL round-bottomed flask. The flask was equipped with a magnetic stir bar and a rubber septum and was flushed with argon. The reaction mixture was stirred at room temperature for 2 h, then the volatiles were evaporated to yield the crude (*R*)-Mosher ester, which was directly analyzed by ^{19}F NMR spectroscopy without purification.

14. GC analysis on a β-Dex column temperature programmed from 130 to 180 °C gave a single peak at 22.35 min (submitters). GC analysis on an Agilent MP-1 column (1909/Z-413E, 30 m x 0.32 mm), temperature ramp 10 °C per min from 50 °C to 315 °C, gave a single peak at 10.61 min (checkers). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 69.03; H, 11.74.

15. The submitters measured $[\alpha]_D^{20}$ –19.5 (c = 1.55, $CHCl_3$) for a run on the same scale and concentration. When they performed the reduction at a ten-fold higher concentration of ketone, the derived alcohol **4** exhibited $[\alpha]_D^{20}$ –16.5 (c = 1.81, $CHCl_3$).

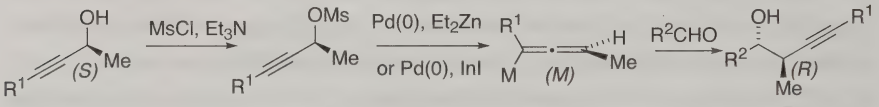
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The palladium-catalyzed conversion of enantioenriched propargylic mesylates such as **2** to enantioenriched allenylzinc (**3**) or indium (**4**) reagents and in situ additions to aldehydes provides a convenient route to homopropargylic alcohol intermediates related to polyketide natural products (Scheme 1).[2,3,4]

Scheme 1. Synthesis of Enantioenriched Homopropargylic Alcohols from Propargylic Mesylates



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1a R^1 = H
1b R^1 = TMS
1c R^1 = TIPS

2a R^1 = H
2b R^1 = TMS
2c R^1 = TIPS

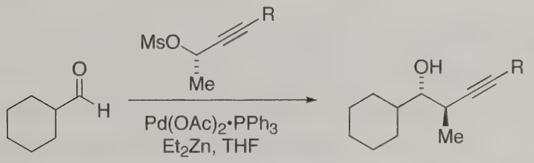
3a/b/c M = Zn(OMs)
4a/b/c M = InI(OMs)

Although the alcohol precursor of mesylate (*S*)-**2a** and its enantiomer are commercially available,[5] their high cost discourages widespread use of the methodology. Accordingly, we have explored simple and economical preparations through use of chiral pool starting materials[6] or lipase resolution of racemic propargylic alcohols for a more cost effective synthesis.[7,8] The TMS reagents **2b**, prepared through lipase resolution of racemic **1b**, show significantly higher diastereoselectivity than the parent alkyne **2a**. While this alternative represents an improvement, the intrinsic inefficiency of optical resolution coupled with the volatility of the resolved alcohols represent significant drawbacks to the methodology. The present procedure employs Noyori asymmetric hydrogenation of alkynyl ketones to prepare the alkynyl TIPS derivative **1c** of 3-butyn-2-ol.[9] This route offers several major advantages compared with the previous approaches to the parent **1a** and the TMS alcohol **1b**:

(1) Unlike alcohol **1a** and its alkynyl TMS analog **1b**, the TIPS compound **1c** is nonvolatile and completely insoluble in water, thereby allowing facile isolation by simple extraction;
(2) all intermediates can be vacuum-dried and purified by short path distillation;
(3) both enantiomers of the chiral catalyst are readily available;
(4) the catalyst precursor can be stored without loss of activity; and,
(5) addition reactions of the derived TIPS allenylzinc reagent to aliphatic aldehydes proceeds readily and with comparable diastereoselectivity to additions of the parent reagent or the TMS derivative.

The outcome of addition reactions of the three allenylzinc reagents generated in situ from mesylates **2a**, **2b**, and **2c** to cyclohexanecarboxaldehyde is summarized in Table 1.

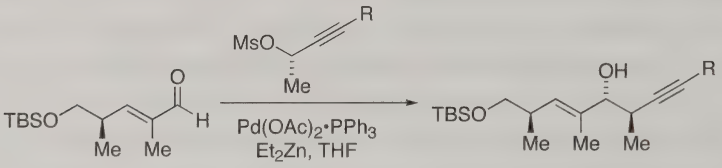
Table 1. Comparison of Addition Reactions of Allenylzinc Reagents Derived in situ from the Mesylate of *(S)*-3-Butyn-2-ol (**2a**) and the Silylated Analogs **2b** and **2c** to Cyclohexanecarboxaldehyde.



R	yield	dr	er
H (**2a**)	86	19:1	99:1
TMS (**2b**)	84	24:1	97:3
TIPS (**2c**)	89	19:1	98:2

An even larger difference in diastereoselectivity for the three reagents was observed with an α-methylated enal (Table 2). Removal of the TIPS group from the adducts is easily effected in minutes with tetrabutylammonium fluoride in THF.

Table 2. Comparison of Addition Reactions of Allenylzinc Reagents Derived in situ from the Mesylate of *(S)*-3-Butyn-2-ol (**2a**) and the Silylated Analogs **2b** and **2c** to a Conjugated Aldehyde.



R	yield	dr
H (**2a**)	71	85:15
TMS (**2b**)	56	88:12
TIPS (**2c**)	80	92:8

1. (a) Department of Chemistry, University of Virginia, PO Box 400319, Charlottesville VA 22904, e-mail jam5x@virginia.edu. (b) Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, curran@pitt.edu.

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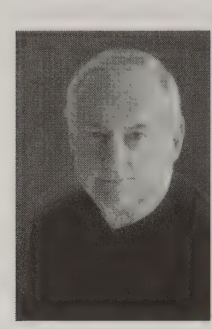
9. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997***, 119,* 8738.

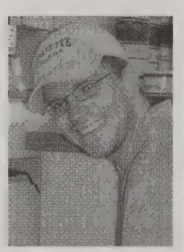
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*rac*)-4-Triisopropylsilyl-3-butyn-2-ol: 3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-: (726202-65-9)
Triisopropylsilyl acetylene: Silane, ethynyltris(1-methylethyl)-; (89343-06-6)
tert-BuLi: Lithium, (1,1-dimethylethyl)-; (594-19-4)
Acetaldehyde; (75-07-0)
4-Triisopropylsilyl-3-butyn-2-one: 3-Butyn-2-one, 4-[tris(1-methylethyl)silyl]-: (183852-48-4)
Manganese Dioxide; (1313-13-9)
RuCl[(*S*,*S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene): Ruthenium, [*N*-[(1*S*,2*S*)-2-(amino-**κ***N*)-1,2-diphenylethyl]-4-methyl-benzenesulfonamidato-**κ***N*]chloro[(1,2,3,4,5,6-**η**)-1-methyl-4-(1-methylethyl)benzene]-; (192139-90-5)
(1*S*,2*S*)-(+)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine: Benzenesulfonamide, *N*,*N*'-(1,2-diphenyl-1,2-ethanediyl)bis[4-methyl-, [*S*-(*R**,*R**)]-; (170709-41-8)
Dichloro(*p*-cymene)ruthenium(II) dimer; (52462-29-0)

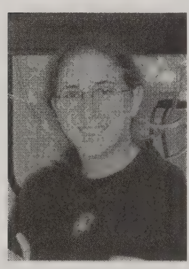
(*S*)-4-Triisopropylsilyl-3-butyn-2-ol: (*S*)-3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-;



James Marshall received a BS degree in Chemistry from the University of Wisconsin PhD degree in 1960 from the University of Michigan with Professor Robert E. Ireland. After two years as an NIH postdoctoral Fellow in the laboratory of William. S. Johnson at Stanford University, he joined the faculty of Northwestern University in 1962 and advanced to the rank of full Professor in 1968. The following year he moved to the University of South Carolina and was subsequently appointed the inaugural Guy Lipscomb Professor of Chemistry. In 1995 he was appointed Thomas Jefferson Professor of Chemistry at the University of Virginia. A central theme in Professor Marshall's research has been the development and application of stereoselective reactions to natural product synthesis.



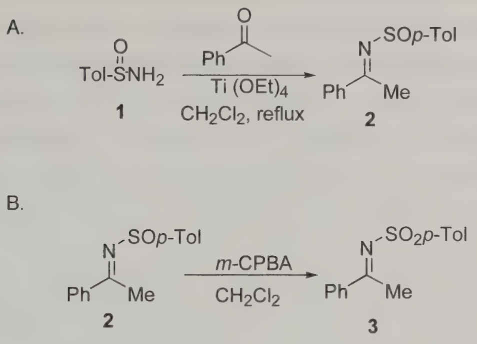
Patrick M. Eidam was born in 1978 in New Castle, PA. Following his graduation with a BS degree in Chemistry from Lafayette College, he entered graduate school at the University of Virginia and joined the research group of Professor James Marshall. He received his PhD degree in 2006 and subsequently obtained a position with the Medicinal Chemistry division at Glaxo Smith Kline in King of Prussia, PA.



Hilary Schenck Eidam was born in 1978 in York, PA. She received a B.S. degree in chemistry from Gettysburg College in 2000 followed by a PhD degree in chemistry from the University of Virginia in the laboratory of Milton Brown. After postdoctoral research with Professor James Marshall at Virginia she joined the Medicinal Chemistry group at Glaxo Smith Kline in King of Prussia, PA.

Kai Zhang was born in China and got his B.S. degree in Chemistry from University of Science and Technology of China in 2005. He came to United States in August 2005 as a graduate student and joined Professor Dennis P. Curran's group at the University of Pittsburgh.

PREPARATION OF *N-p*-TOLYLSULFONYL-(*E*)-1-PHENYLETHYLIDENEIMINE



Submitted by José Luis García Ruano, José Alemán, Alejandro Parra, and M. Belén Cid.[1]
Checked by Kounosuke Oisaki and Masakatsu Shibasaki.

1. Procedure

A. N-p-Tolylsulfinyl-(E)-1-phenylethylideneimine (**2**). An oven-dried 300-mL two-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirring bar, and a rubber septum, is charged with *N-p*-toluenesulfinamide **1** (Note 1) (5.2 g, 33.5 mmol, 1.0 equiv), acetophenone (8.0 mL, 68.5 mmol, 2.0 equiv) (Note 2), and $Ti(OEt)_4$ (35 mL, 168 mmol, 5.0 equiv) (Note 3) by temporarily removing the septum. A vacuum adaptor is attached to the condenser and the reaction mixture is stirred under vacuum (1 mmHg) for 15 min. A balloon of argon is attached to the adapter at the top of the condensor. The solid is dissolved in CH_2Cl_2 (75 mL), which is added via syringe through the septum (Note 4). The solution is heated under reflux for 36 h (external bath temperature 80 °C and internal temperature 40 °C), and the reaction is monitored by TLC (Note 5). After cooling the solution to 0 °C using an ice bath, MeOH (50 mL), CH_2Cl_2 (50 mL) and a saturated solution of $NaHCO_3$ (7 mL) are sequentially added with vigorous stirring until precipitation of titanium salts is observed. The solid is vacuum filtered (25 mmHg) through a Büchner funnel (Note 6) and washed with CH_2Cl_2 (3 x 75 mL). The organic phase is dried over anhydrous Na_2SO_4, filtered into a single-necked, 500-mL round-bottomed flask and concentrated by rotary evaporation (25 °C, 10 mmHg) to afford a yellow oil, which is charged onto a silica gel column (8 cm x 18 cm) (Note 7). While collecting fractions of 50 mL, the column is eluted with AcOEt/hexanes (10:90) until acetophenone has completely emerged (volumes of eluents used = 0.6 L). The elution is then continued with AcOEt/hexanes (50:50). The product-containing fractions (total volume of eluent used for this product = 1.7 L) are concentrated and successively recrystallized from CH_2Cl_2/hexanes to afford *N*-sulfinylketimine **2** (5.78 g, 67%) as a white solid (Notes 8 and 9).

B. N-p-Tolylsulfonyl (E)-1-phenylethylideneimine (**3**). Into a round-bottomed 300-mL flask equipped with a magnetic stirring bar is added *N-p*-tolylsulfinylketimine **2** (5.2 g, 20 mmol, 1.0 equiv) and CH_2Cl_2 (75 mL) (Note 10). The solution is cooled to 0 °C (Note 11) and commercially available *m*-CPBA (4.5 g, 20 mmol, 1.0 equiv) (Note 12) is added slowly (portions of 1.0 g per min) to the solution, which is open to the atmosphere. The mixture is allowed to warm to room temperature and the reaction is monitored by TLC (Note 13). After five min, the mixture is diluted with CH_2Cl_2 (50 mL), transferred to a separatory funnel, washed with a saturated solution of $NaHCO_3$ (5 x 25 mL) (Note 14), and the organic phase is dried over anhydrous Na_2SO_4. The solution is filtered into a single-necked, 300-mL round-bottomed flask and concentrated by rotary evaporation (25 °C, 10 mmHg) to afford crude **3** as a white solid, which is diluted with 7 mL of CH_2Cl_2 and charged on a silica gel column (150 g, 5.5 cm x 18 cm) (Note 7). The column is eluted initially with AcOEt/hexanes (10:90) until the *N*-sulfinylketimine **2** emerges, and then the elution is then continued with AcOEt/hexanes (10:50). The product-containing fractions are concentrated to afford *N*-sulfonylketimine **3** (4.23 g, 77%) as a white solid (Notes 14, 15 and 16).

2. Notes

1. *N*-Sulfinamide **1** could be purchased from Aldrich Chemical Company, Inc. in optically pure form. However, (±)-**1** can be obtained at much lower cost following a known procedure,[11] which involves two steps from *p*-tolyldisulfide.

2. Acetophenone, 99% was purchased from Aldrich Chemical company, Inc. and was used without further purification.

3. Titanium (IV) ethoxide, technical grade was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

4. No difference in the yield was observed when using either dried CH_2Cl_2 (from P_2O_5) or the directly purchased CH_2Cl_2 from SDS (purex analytical grade).

5. The reaction was monitored by TLC on silica gel using hexanes/EtOAc (2:1) as eluent and visualization with phosphomolibdic acid. The starting material **1** had $R_f = 0.1$ (green), acetophenone had $R_f = 0.77$ (green), and the final product **2** had $R_f = 0.38$ (brown).

6. A double filter paper of medium porosity was used.

7. Silica gel (230–400 mesh) from Merck was used.

8. The physical properties of *N*-sulfinylketimine **2** were as follows: white solid, mp 95.0–96.0 ºC (lit.[2] mp 99–100 ºC). ^1H NMR (500 MHz) δ: 2.40 (s, 3 H) 2.78 (s, 3 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.47 (t, *J* = 6.7 Hz, 1 H), 7.72 (d, *J* = 8.2 Hz, 2 H), 7.88 (d, *J* = 7.6 Hz, 2 H), ^{13}C NMR (125.7 MHz) δ: 20.2, 21.4, 125.2, 127.5, 128.4, 129.8, 131.8, 138.2, 141.8, 143.3, 173.9; IR (KBr, cm^{-1}): 3430, 1637, 1565, 1096; LRMS (ESI-MS) *m/z* 258 $(M+H)^+$, 280 $(M+Na)^+$; HRMS (FAB-MS) calcd for $C_{15}H_{16}NOS$ $(M+H)^+$ 258.0947, found 258.1008.

9. *N*-Sulfinylketimine **2** and *N*-sulfonylketimine **3** are hydrolyzed upon extended contact with silica gel; therefore the flash chromatography should be carried out rapidly.

10. In this case, dry CH_2Cl_2 (distilled from P_2O_5) was used, since traces of water can hydrolyze the starting material **2** or *N*-sulfonylketimine **3**.

11. This reaction was exothermic, therefore the addition should be carried out at 0 °C. Without an ice bath (0 °C) an increase in temperature from 21 to 40 °C was detected.

12. 3-Chloro-perbenzoic acid (>77 %) was purchased from Aldrich Chemical Company, Inc. (Lot number S22939 was used, which contained 18.03 % of water and 71.70 % of 3-chloroperbenzoic acid). The reagent was directly used without removal of the water, which resulted in a 78% yield. The yield of the reaction could be increased to 84% when water was removed from this reagent. The procedure for removing water was as follows: Prior to its use, water was removed by dissolving the commercial

product in CH_2Cl_2, drying the organic solution over anhydrous Na_2SO_4, filtering and concentrating the reagent to dryness under vacuum. Titration following the procedure reported in the literature (McDonald, R. N.; Steppel, R. N.; Dorsey, J. E. *Org. Synth.* **1970**, *50*, 15) indicated a purity of 90% (using $Na_2S_2O_3$ 0.1004 N). A purity of 91% was obtained when the purity determination was carried out by HPLC: performed on ZORBAX RX-C8 (4.6 mm x 25 cm) with 50:50 water:methanol, with a flow rate of 0.5 mL/min at 210 nm (3-chlorobenzoic acid t_R= 5.5 min, 3-Chloroperbenzoic acid t_R= 21.5 min). When a calibration standard was used (3-chlorobenzoic acid at different concentrations) under these conditions, the purity was determined to be 90%.

13. The reaction was monitored by TLC on silica gel using hexanes/EtOAc (2:1) as eluent and visualization with a phosphomolibdic acid. The starting material **2** has an R_f= 0.38 while R_f= 0.70 for the final product **3**.

14. *N*-Sulfonylketimine **3** is hydrolyzed upon extended contact with water; therefore, the washes should be carried out rapidly.

15. The physical properties of *N*-sulfonylketimine **3** were as follows: white solid, mp 88.5–90.5 °C (lit.[10k] mp 88–90 °C). ^{1}H NMR (500 MHz) δ: 2.45 (s, 3 H) 2.99 (s, 3 H), 7.34 (d, J = 8.2 Hz, 2 H), 7.41 (t, J = 8.0 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 21.1, 21.5, 127.0, 128.2, 128.6, 129.4, 133.1, 137.5, 138.7, 143.5, 179.8; IR (KBr, cm^{-1}): 3435, 1590, 1570, 1286, 1180, 1083; LRMS (ESI-MS) *m/z* 274 $(M+H)^+$, 296 $(M+Na)^+$; HRMS (FAB-MS) calcd for $C_{15}H_{16}NO_2S$ $(M+H)^+$ 274.0896, found 274.0775. The purity of the sample was determined by HPLC (>98%), performed on Chiral AS (Daicel) with 60:40 hexane:2-propanol and a flow rate of 0.6 mL/min.

16. The *N*-sulfonylketimine **3** (0.007 mol, 2 g) could be crystallized from Et_2O (80 mL). The solution was heated until the solid dissolved, and filtered through filter paper of medium porosity. The solution was kept for 12 h at –20 °C. White needles were collected using a Büchner funnel under vacuum (25 mmHg), which resulted in the isolation of 1.90 g of pure **3** (95% yield).

Safety and Waste Disposal Information

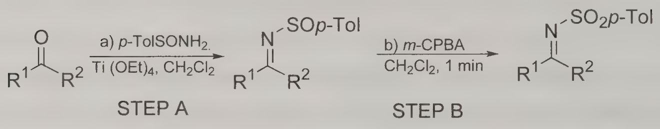
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

As the sulfonyl moiety has proven to be a powerful activating group of iminic C=N bonds, *N*-sulfonyl imines have been widely used in organic synthesis.[3] They are excellent substrates in aza Diels-Alder reactions,[4] nucleophilic additions,[5] reductions,[6] as well as in radical[7] or ene[8] reactions. They have been also used in the synthesis of aziridines.[9]

Despite the plethora of methods reported for obtaining *N*-sulfonyl imines,[10] most of the methods are only efficient in preparing those compounds derived from aromatic or non-enolizable aldehydes. Therefore, it was necessary to find a new general protocol for synthesizing any *N*-sulfonyl aldimine or ketimine, even those containing enolizable α-hydrogens. We have recently reported a new procedure that fulfills all of these requirements.[11] The procedure involves the condensation of carbonyl compounds with *p*-tolyl (Table 1) and *tert*-butyl (Table 2) sulfinamides followed by oxidation of the resulting *N*-sulfinylimines with *m*-CPBA. The method is applicable to aldehydes (aliphatics and aromatics) and ketones (dialkyl, diaryl, and alkyl aryl), even those containing enolizable protons. The configurations of α-stereogenic centers are not affected and the method is highly selective in the presence of C=N and C=C (deactivated or not) double bonds. The new procedure has been applied to the preparation of compounds collected in Table 1. The main advantages of this procedure derive from the near absence of structural limitations for the starting carbonyls used for preparing sulfinylimines, as well as the higher stability of these sulfinylimines (they can be stored without significant decomposition for long periods of time) with respect to their corresponding sulfonylimines.

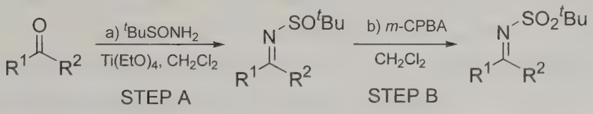
Table 1. Preparation of *N*-*p*-Tolylsulfonylimines.



Entry	R^1	R^2	Reaction Yields (%)		
			Step A	Step B	Overall
1	Ph	H	93	100	93
2	3-$MeOC_6H_4$	H	92	100	92
3	2-Napht	H	94	95	89
4	2-BrC_6H_4	H	91	100	91
5	4-CNC_6H_4	H	81	85[a]	69
6	$PhCH{=}CH_2$	H	80	95	76
7	*n*-Pr	H	78	96[b]	75
8	*i*-Pr	H	65	100[b]	65
9	*t*-Bu	H	79	96	76
10	Ph	Ph	79	88	69
11	4-$MeOC_6H_4$	Me	73	84	61
12	4-CNC_6H_4	Me	77	90	69
13	*t*-Bu	Me	48	90	43
14	*i*-Pr	Me	64	90	58

[a] In this case the reaction time was 15 min. [b] To avoid oxaziridine formation, this reaction was carried out at 45 °C.

Table 2. Preparation of *N*-*t*-Butylsulfonylimines.



Entry	R^1	R^2	Reaction yields (%)		
			Step A	Step B	Overall
1	Ph	H	96	100	96
2	2-furyl	H	63	100	63
3	*n*-Pr	H	100	84	84
4	Ph	Ph	75	100	75
5	Ph	Me	63	100	63
6	4-$MeOC_6H_4$	Me	62	100	62
7	4-CNC_6H_4	Me	73	100	73
8	-$(CH_2)_5$-		65	90	59
9	Et	Me	73[a]	78	57
10	2-pyridyl	Me	59[b]	80	47

[a] A 4:1 mixture of the E/Z isomers was formed. [b] In this case the reaction time was 15 m.

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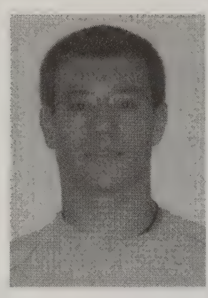
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

N-*p*-Toluenesulfinamide: Benzenesulfinamide, 4-methyl-; (6873-55-8)
Acetophenone: Ethanone, 1-phenyl-; (98-86-2)
$Ti(OEt)_4$: Ethanol, titanium(4+) salt; (3087-36-3)
N-*p*-Tolylsulfinyl-(*E*)-1-phenylethylideneimine: Benzenesulfinamide, 4-methyl-*N*-(1-phenylethylidene)-, [*N*(*E*)]-; (177468-94-9)
m-CPBA: Benzenecarboperoxoic acid, 3-chloro-; (937-14-4)
N-*p*-Tolylsulfonyl-(*E*)-1-phenylethylideneimine: Benzenesulfonamide, 4-methyl-*N*-(1-phenylethylidene)-, (*E*)-; (163586-87-6)

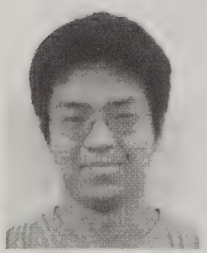
José Luis García Ruano received his Ph.D. at the Universidad Complutense (Madrid, 1973). He has held appointments as a visiting Professor at the Florida State (1992) and Emory (2003) Universities and received a fellowship with the JSPS in 2006. He was appointed Full Professor in Organic Chemistry at Universidad Autónoma de Madrid in 1982 and has served as Vice-president of the Spanish Royal Society of Chemistry for 4 years. His research interests are centered in the chemistry of sulfoxides and related compounds and their applications in asymmetric synthesis. In these fields, he has published approximately 300 papers and supervised thirty-five Ph.D. theses.

José Alemán received his B.Sc. in Chemistry at the Universidad Autónoma of Madrid (Spain) in 2000. In 2003 he spent six months in the laboratory of Prof. Albert Padwa at Emory University (Atlanta, USA) working on Pummerer rearrangements. In 2005 he received the Lilly Research Award for Ph. D. students and presented his Ph. D. thesis, which focused on remote stereocontrol by sulfinyl groups and was supervised by Prof. Jose Luis García Ruano. He is currently working (2006) as post-doctoral researcher with Prof. Karl Anker Jørgensen (Aarhus, Denmark). His research interests include asymmetric synthesis, sulfur chemistry and organocatalysis.



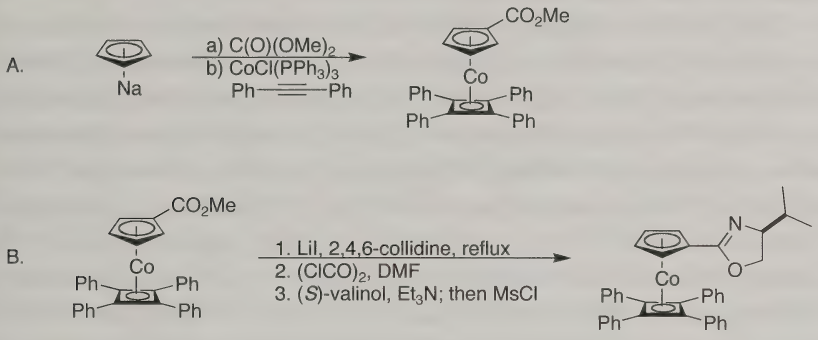
Alejandro Parra was born in Toledo, Spain. He received a B.S. degree in chemistry at the Universidad Autónoma of Madrid (Spain) in 2004. He is now pursuing his Ph.D. at the Universidad Autónoma de Madrid under the supervision of Prof. José Luis García Ruano. His research concerns asymmetric synthesis with sulfur compounds. He is currently a predoctoral research fellow in the laboratory of Prof. Andrew Myers at Harvard University (USA) working on the chemistry of tetracyclines.

M. Belén Cid was born in Madrid, Spain, in 1967. She received her Ph.D. degree (1995) under the supervision of Professors J. L. García Ruano and M. Carmen Carreño at the Autonoma University of Madrid. She joined the group of Prof. Gerald Pattenden (1996-1999) at the Nottingham University as a postdoctoral fellow. Following two stays in the groups of Prof. Manuel Martín-Lomas (1999-2001) in Seville (CSIC) and Prof. Serafín Valverde (2002-2003) in Madrid (CSIC), she returned to Prof. García Ruano's group in 2004. Her research interests are focused on the development of highly stereoselective methods from sulfur compounds, synthesis of pharmacologically active compounds and asymmetric organocatalysis.



Kounosuke Oisaki was born in 1980 in Tokushima, Japan. He received his B.S. in 2003 and M.S. in 2005 from The University of Tokyo. Presently, he is pursuing his Ph.D. degree at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, under the guidance of Professor Masakatsu Shibasaki. His research interests are in the area of asymmetric synthesis and catalysis.

PREPARATION OF (η^5-(*S*)-2-(4-METHYLETHYL)-OXAZOLINYLCYCLOPENTADIENYL)-(η^4-TETRAPHENYLCYCLO-BUTADIENE)COBALT
(Cobalt, [1,1',1'',1'''-(η^4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]][(1,2,3,4,5-η)-1-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-2,4-cyclopentadien-1-yl])



Submitted by Carolyn E. Anderson, Larry E. Overman,*[1] Christopher J. Richards, Mary P. Watson and Nicole White.
Checked by Joshua Bolger and Marvin J. Miller.

1. Procedure

A. Preparation of (η^5-carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt. A flame-dried, 500-mL, three-necked, round-bottomed flask is fitted with a stirring bar, reflux condenser, rubber septa, and an argon inlet. The flask is flushed with dry argon and charged with sodium cyclopentadienide (Note 1) (20 mL, 2.0 M in THF, 40 mmol) and 20 mL of anhydrous tetrahydrofuran (Note 2) via syringe. Dimethyl carbonate (Note 1) (10.2 mL, 120 mmol) is added via syringe and the resulting solution is warmed to reflux for 4 h before cooling to room temperature (Note 3).

Once cooled, 160 mL of toluene (Note 2) is added via syringe, followed by chlorotris(triphenylphosphine)cobalt(I) (Note 4) (30.8 g, 34.8 mmol) and diphenylacetylene (Note 5) (14.2 g, 80 mmol) by temporarily removing a rubber septum. The resulting mixture is heated at reflux for 5 h before cooling to room temperature, transferring to a single-neck flask, and concentrating under reduced pressure. The residue is suspended in hexanes (150 mL) and filtered through a Büchner funnel. The solids are washed with hexanes (~3.5 L) until the filtrate is colorless. The resultant dark mustard-colored filter cake is dissolved from the filter into a new collection flask with methylene chloride. Washing is continued until the filtrate is colorless. A black insoluble solid is left after washing and is discarded. The organic solution is concentrated *in vacuo* to provide 12.7 g (23.6 mmol, 67%) of (η^5-carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt as a mustard-colored solid (Notes 6, 7).

B. Preparation of (η^5-(S)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt. A flame-dried, 250-mL, round-bottomed flask is fitted with an air condenser, stirring bar and an argon inlet. The flask is flushed with dry argon and then charged with (η^5-carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (10 g, 18.6 mmol), lithium iodide (Note 8) (4.95 g, 37.2 mmol), and 100 mL of 2,4,6-collidine (Note 1) by temporarily removing the condenser. The resulting solution is warmed to reflux. After 16 h, the solution is cooled to room temperature (Note 9) and diluted with 50 mL of methylene chloride. This solution is washed with 150 mL of 2 N aqueous hydrochloric acid, and the aqueous layer is extracted with 150 mL of methylene chloride. The combined organic phases are then washed with 2 N aqueous hydrochloric acid (4 x 150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide (η^5-carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt as an orange solid (Note 10), which is used directly in the next transformation.

A flame-dried, 250-mL, round-bottomed flask is fitted with a stirring bar and an argon inlet. The flask is flushed with argon and then charged with crude (η^5-carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)-cobalt and 124 mL of methylene chloride (Note 2). Oxalyl chloride (Note 1) (3.25 mL, 37.2 mmol) and dimethylformamide (Note 11) (3 drops) are added sequentially. Upon addition of the latter, gas evolution is observed. The resulting solution is maintained at room temperature. After 30 min, the solution is concentrated using a rotary evaporator. Volatile byproducts and excess starting materials are removed by dissolving the residue in 100 mL of methylene chloride and concentrating this solution using a rotary evaporator. The evaporation procedure is repeating three times to provide the corresponding acid chloride as a red-brown residue, which is used directly in the next transformation.

A flame-dried, 500-mL, round-bottomed flask is fitted with a stirring bar and a septum containing argon inlet and outlet needles. The flask is flushed with argon and then charged with (*S*)-valinol·HCl salt (Note 12) (3.6 g, 26 mmol) by temporarily removing the septum, triethylamine (Note 11) (15.5 mL, 112 mmol) and 86 mL of methylene chloride (Note 2) via syringe. A solution of crude acid chloride and 100 mL of methylene chloride (Note 2) is added to the flask via cannula. The resulting solution is maintained at room temperature, and, after 2 h, the solution is cooled to 0 °C using an ice/water bath. Methanesulfonyl chloride (Note 1) (3.6 mL, 47 mmol) is then added in one portion via syringe, and the resulting solution is allowed to warm to room temperature. After 16 h, the solution is transferred to a separatory funnel and washed with 150 mL of saturated aqueous sodium bicarbonate and 150 mL of brine. The organic layer is then dried over anhydrous sodium sulfate, filtered, and concentrated using a rotary evaporator. The residue is dissolved in a minimum volume of methylene chloride (~50 mL) and purified through a column of silica gel using 9:1 hexanes-ethyl acetate as eluent (Note 13). Evaporation of solvent gives 8.2 g (13.9 mmol, 75% yield) of (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt as a yellow solid (Note 14).

2. Notes

1. Sodium cyclopentadienide was purchased from Aldrich Chemical Company or Strem Chemical. This reagent should be light red/orange in color. Commercial reagent that is black in color and/or contains some solid residue should not be used. Dimethyl carbonate, oxalyl chloride, methanesulfonyl chloride, and 2,4,6-collidine were purchased from Acros Organics or Aldrich Chemical Company. These chemicals were used as received.

2. Tetrahydrofuran, toluene and methylene chloride were purified by passage through activated alumina using a GlassContour solvent purification system.[2] The checkers used anhydrous Acroseal solvents.

3. Sodium carbomethoxycyclopentadienide can be isolated,[3] but its isolation and purification were unnecessary for this procedure.

4. Chlorotris(triphenylphosphine)cobalt(I) was prepared according to a detailed literature procedure.[4] This reagent could be purchased from Aldrich Chemical Company. However, it is quite expensive; the use of the commercial material typically resulted in lower yields of product.

5. Diphenylacetylene was purchased from Acros Organics and was recrystallized from ethanol prior to use.

6. Somewhat higher yield (13.8 g, 25.6 mmol, 74%) was observed when the solution of sodium carbomethoxycyclopentadienide and THF was transferred by cannula to a 500-mL round-bottomed flask charged with dichlorotris(triphenylphosphine)cobalt(I), diphenylacetylene and toluene. However, this procedure was less convenient.

7. The product, (η^5-carbomethoxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt, showed the following characterization data; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.23 (s, 3 H), 4.79 (t, J = 2.0 Hz, 2 H), 5.21 (t, J = 2.0 Hz, 2 H), 7.22–7.30 (m, 12 H), 7.43–7.45 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.4, 76.5, 84.7, 86.6, 86.8, 126.9, 128.2, 129.0, 135.3, 166.6; Infrared spectrum (thin film) cm^{-1}: 3058, 2953, 1713, 1596, 1498, 1467, 1281, 1140; HRMS (FAB+) *m/z* 538.1320 [538.1343 calcd for $C_{35}H_{27}O_2Co$ (M^+)]; Anal. Calcd. for $C_{35}H_{27}O_2Co$: C, 78.06; H, 5.05. Found: C, 78.30; H, 5.43.

8. Lithium iodide was purchased from Acros Organics. In some instances, the use of old bottles of this reagent resulted in incomplete conversion.

9. The disappearance of starting material could be monitored by TLC analysis. Using 20% ethyl acetate: hexanes as eluent, (η^5-carbomethoxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt had an R_f of 0.8.

10. The crude product, (η^5-carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt, showed the following ^{1}H NMR spectrum; (500 MHz, $CDCl_3$) δ: 4.84 (2d, J = 2.0 Hz, 2 H), 5.23 (2d, J = 2.0 Hz, 2 H), 7.20–7.24 (m, 12 H), 7.42–7.44 (m, 8 H).

11. Dimethylformamide and triethylamine were purified by passage through GlassContour solvent purification columns.[2] The checkers used anhydrous dimethylformamide purchased from Acros Organics. Triethylamine was purchased from Aldrich Chemical Company and used as received.

12. (*S*)-Valinol was prepared by reduction of (*S*)-valine.[5] The checkers used (*S*)-valinol purchased from Aldrich Chemical Company, Inc. The salt was formed by treatment of the freebase with 2 N HCl in diethylether.

13. The submitters reported dissolving the crude residue in 9:1 hexanes:EtOAc prior to loading on the column, but the checkers isolated 5.6

g (9.5 mmol, 51% yield) of pure product by filtration of the resulting slurry. The residue remaining after concentration of the filtrate was dissolved in a minimum of methylene chloride and purified as described to give an additional 2.6 g (4.4 mmol, 24% yield) of the pure product. Subsequent reactions were purified exclusively by column chromatography.

14. The product, (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt, shows the following characterization data; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.76 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.37–1.44 (m, 1 H), 3.41–3.55 (m, 3 H), 4.71 (2d, *J* = 2.5 Hz, 2 H), 4.8 (2d, *J* = 2.5 Hz, 2 H), 5.09 (s, 1 H), 5.25 (brs, 1 H) 7.20–7.29 (m, 12 H), 7.45–7.47 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.4, 19.6, 33.0, 69.5, 72.7, 76.0, 82.0, 84.4, 85.0, 86.4, 126.4, 128.0, 129.0, 135.4, 160.5; Infrared spectrum (thin film) cm^{-1}: 3058, 2958, 1652, 1597, 1499, 1373, 1113, 1024; HRMS (FAB+) *m/z* 592.2055 [592.2051 calcd for $C_{39}H_{35}CoNO$ (M+H)]. Anal. Calcd. for $C_{39}H_{34}ONCo$: C, 79.17; H, 5.79; N, 2.37. Found: C, 79.12; H, 5.83; N, 2.33.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This synthesis of (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt is a modification of a procedure originally reported by Richards and Stevens.[6] The procedure has been streamlined and modified to enable large-scale preparation of this oxazoline. Nucleophilic conditions, rather than hydrolytic, are used to cleave the ester to the acid in Step B, thereby eliminating the use of DMSO, which is difficult to remove. Removal of DMSO is an essential feature of the original procedure as oxalyl chloride is employed in the following step.[6] In the present procedure, the oxazoline is formed directly from the crude valinol amide by reaction with methanesulfonyl chloride and triethylamine in methylene chloride. These conditions eliminate the need for toxic carbon tetrachloride; previously the isolated valinol amide was cyclized using triphenylphosphine, carbon tetrachloride and triethylamine.[6] In this optimized procedure, conversion of the ester to the oxazoline is accomplished in one pot.

(η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt is an intermediate in the synthesis of the planar, chiral palladium(II) catalysts, [COP-Cl]$_2$,[7] [COP-OAc]$_2$[7] and COP-hfacac,[7] which have been used in the catalytic asymmetric synthesis of chiral allylic amides[8,9] and allylic esters.[10] This procedure illustrates a general synthesis of enantiopure (η^5-(*S*)-2-oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt complexes. Analogous oxazoline complexes prepared from (*S*)-serine have been used as ligands for catalytic asymmetric addition of organozinc reagents to aldehydes and palladium-catalyzed allylic alkylations.[11] As enantioenriched monodentate oxazolines have found use as chiral ligands,[12] and η^5-(cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt complexes have been used to prepare a variety of novel materials,[13] the oxazoline product of this procedure could find use in its own right.

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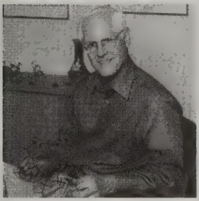
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

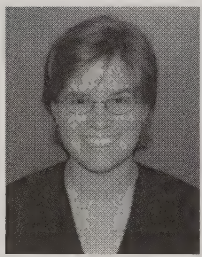
(η^5-Carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt; (182627-81-2)
Sodium cyclopentadienide: Sodium, 2,4-cyclopentadien-1-yl-; (4984-82-1)
Chlorotris(triphenylphosphine)cobalt(I); (26305-75-9)
Diphenylacetylene: Benzene, 1,1'-(1,2-ethynediyl)bis-; (501-65-5)
Lithium iodide; (10377-51-2)
2,4,6-Collidine: Pyridine, 2,4,6-trimethyl-; (108-75-8)
Oxalyl Chloride: Ethanedioyl dichloride; (79-37-8)
N, *N*-Dimethylformamide; (68-12-2)
(*S*)-Valinol: 1-Butanol, 2-amino-3-methyl-, (2*S*)-; (2026-48-4)
Triethylamine: Ethanamine, *N,N*-diethyl-; (121-44-8)
Methanesulfonyl chloride; (124-63-0)



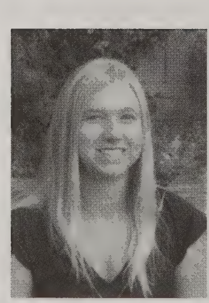
Larry Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971 where he is now Distinguished Professor of Chemistry. Professor Overman was Chair of the UC Irvine Department of Chemistry from 1990–1993.

Carolyn Anderson received her B.Sc. degree in Chemistry from the University of Michigan in 1998 and her Ph.D. in Chemistry from the University of California at Irvine (with Larry Overman) in 2003. She was a Dreyfus Postdoctoral Fellow at Pomona College (Claremont, California) under the mentorship of Daniel O'Leary (2004–2006). In 2006, she joined the faculty of Calvin College (Grand Rapids, Michigan) as an Assistant Professor of Chemistry. Her current research interests include using organometallic methods to synthesize libraries of strained carbocycles.

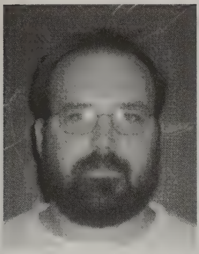
Chris Richards was born in Woking, England, and obtained a B.Sc degree in Chemistry from the University of Bath in 1989. This was followed by a Ph.D. in 1990 working with Professor Sue Gibson at the University of Warwick. After spending 1 year as an Alexander von Humboldt Research Fellow with Professor Helmchen at the University of Heidelberg, he took up a Lectureship at Cardiff University in Wales. In 2001 he moved to his current position of Reader at Queen Mary, University of London. His research interests encompass organometallic chemistry, organic synthesis, stereochemistry and catalysis.



Mary P. Watson received her B.A. from Harvard University in 2000, where she studied organic chemistry under the direction of Prof. David Evans. She then moved to University of California, Irvine, to work with Prof. Larry Overman. Her graduate research focused on the palladium(II)-catalyzed asymmetric allylic imidate rearrangement, including mechanistic studies performed in collaboration with Prof. Robert Bergman at the University of California, Berkeley. During her graduate work, she received the Allergan graduate student fellowship. She received her Ph.D. in 2006 and is currently a postdoctoral researcher at Harvard University with Prof. Eric Jacobsen.

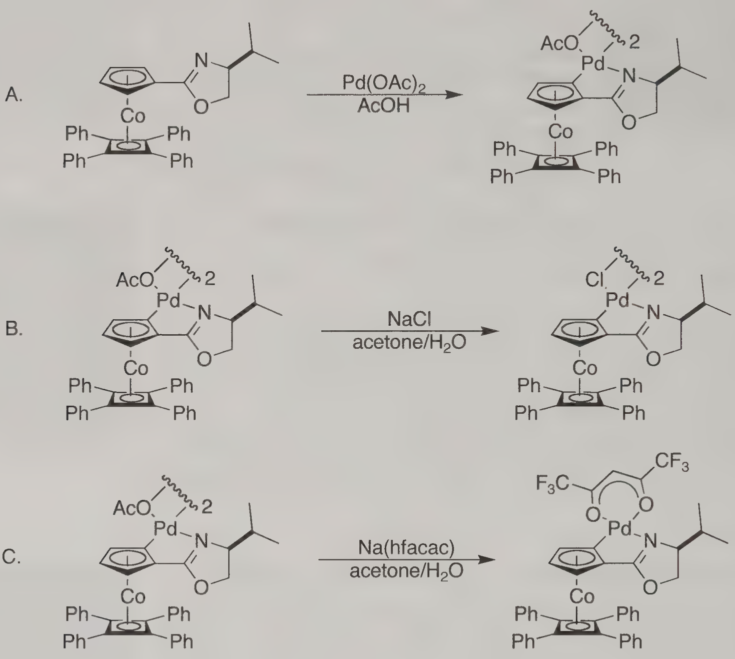


Nicole S. White received her B.S. from the University of California, San Diego, in 2002. She then accepted a position in the medicinal chemistry department of Neurocrine Biosciences, where she worked on development of an MC4 antagonist aimed towards the treatment of cachexia. In 2004 she moved to the University of California, Irvine, to work with Prof. Larry Overman. Currently, her graduate research focuses on the use of palladium(II) catalysts to construct carbon–heteroatom bonds asymmetrically.



Joshua Bolger received his B.S. in chemistry from the Rochester Institute of Technology in 2000. While at RIT he worked as an intern at AstraZeneca, synthesizing CNS active molecules, and Eastman-Kodak Company, synthesizing photosensitizing dyes for silver-halide film. After receiving his B.S. he joined OSI Pharmaceuticals, Inc. where he worked on a number of projects in the fields of Diabetes/Obesity and Oncology. In 2003 Joshua began his graduate education joining the laboratory of Dr. Marvin J. Miller at the University of Notre Dame. He is currently in his fourth year of research focusing on the synthesis of bioactive molecules using Acylnitroso Diels-Alder reactions.

PREPARATION OF THE COP CATALYSTS: [(*S*)-COP-OAc]$_2$, [(*S*)-COP-Cl]$_2$, AND (*S*)-COP-hfacac



Submitted by Carolyn E. Anderson, Stefan F. Kirsch, Larry E. Overman,*[1] Christopher J. Richards and Mary P. Watson.
Checked by Brian S. Bodnar and Marvin J. Miller.

1. Procedure

A. Preparation of di-μ-acetatobis[(η^5-(S)-(pR)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-C, 3'-N)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium ([COP-OAc]$_2$). A flame-dried, single-necked, 250-mL round-bottomed flask is fitted with a stirring bar and an argon inlet. The flask is evacuated, refilled with argon and then, while temporarily removing the argon inlet, charged with (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)-cobalt (9.6 g, 16.2 mmol)[2] and 96 mL of glacial acetic acid. Palladium(II) acetate (Note 1) (3.6 g, 16.2 mmol) is then added. The red solution is then

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heated at 95 °C (oil bath temperature) and the formation of an orange precipitate is observed. After 30 min, the solution is cooled to room temperature and filtered to provide an orange solid. This solid is washed with 50 mL of glacial acetic acid and dried under vacuum to provide 8.9 g (5.9 mmol, 73% yield) of di-μ-acetatobis[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium as a mustard-colored solid (Note 2).

B. Preparation of di-μ-chlorobis[(η^5-(S)-(pR)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-C, 3'-N)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium ([COP-Cl]$_2$). A single-necked, 250-mL round-bottomed flask is fitted with a stirring bar. The flask is charged with di-μ-acetatobis[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium (8.9 g, 5.9 mmol) and 59 mL of acetone. Aqueous sodium chloride (2 M, 30 mL) is then added, and the resulting heterogeneous mixture is stirred at room temperature (Note 3). After 4 h, the yellow solid is collected by filtration of the reaction mixture. This solid is washed with 125 mL of water followed by 20 mL of acetone and then dried under vacuum to provide 8.2 g (5.6 mmol, 95% yield) of di-μ-chlorobis[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenyl-cyclobutadiene)cobalt]dipalladium, [COP-Cl]$_2$, as a mustard-colored solid (Notes 4, 5, 6).

C. Preparation of hexafluoroacetylacetonate[(η^5-(S)-(pR)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-C, 3'-N)(η^4-tetraphenylcyclobutadiene)cobalt]palladium (COP-hfacac). A single-necked, 25-mL round-bottomed flask is equipped with a stir bar and charged with [COP-OAc]$_2$ (1.0 g, 0.66 mmol), sodium hexafluoroacetylacetonate (Note 7) (1.6 g, 6.8 mmol), 6.6 mL of acetone and 3.3 mL of water. The mixture is stirred vigorously at room temperature (Note 3). After 9 h, the mixture is filtered, and the filter cake is washed with 10–20 mL of water and then dried over P_2O_5 in a vacuum dessicator for 12 h to provide 1.1 g (1.2 mmol, 91%) of hexafluoroacetylacetonate[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)-cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]-palladium, COP-hfacac, as an orange solid (Notes 8, 9).

2. Notes

1. Palladium acetate should be an orange/red solid. It can be obtained from either Strem Chemicals or Aldrich Chemical Co. In one instance, the submitters report that a commercial sample gave poor results; good results were obtained when this sample of palladium acetate was purified by crystallization from benzene.

2. Characterization data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: –0.01 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 0.46 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.72–1.81 (m, 1 H, C*H*), 1.96 (s, 3 H, C*H*$_3$), 2.98 (td, *J* = 9.0, 3.1 Hz, 1 H, C*H*), 3.36 (t, *J* = 9.0 Hz, 1 H, C*H*$_2$), 4.08 (dd, *J* = 8.6, 3.9 Hz, 1 H, C*H*$_2$), 4.23 (t, *J* = 2.4 Hz, 1 H, C*H*), 4.62 (d, *J* = 1.4 Hz, 1 H, C*H*), 4.68 (d, *J* = 2.0 Hz, 1 H, C*H*), 7.20–7.29 (m, 12 H, Ar*H*), 7.64 (m, 8 H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.3, 18.8, 24.2, 29.1, 65.0, 71.2, 76.2, 79.4, 85.0, 85.4, 86.8, 98.1, 126.2, 128.1, 129.5, 136.1, 170.8, 180.9; Infrared spectrum (thin film) cm^{-1}: 3061, 2961, 1583, 1502, 1417, 1366, 1181, 1069. Anal. Calcd. for $C_{82}H_{72}O_6N_2Co_2Pd_2$: C, 65.04; H, 4.93; N, 1.85. Found: C, 64.81; H, 4.74; N, 1.98.

3. An aliquot was removed and filtered. The solid was analyzed by ^{1}H NMR spectroscopy to determine when the reaction was complete, which typically required 4 h.

4. The checkers found that the sample could be purified by filtration through a short plug of silica gel using methylene chloride as the eluent to afford the product as an orange solid (99% yield before purification, 97% yield after purification). The product, di-μ-chlorobis[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium, exists as a 1.0:0.7 mixture of dimers in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.70–0.74 (m, 6 H, C*H*$_3$), 0.76 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 0.80 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 2.20–2.33 (m, 2 H, CH), 3.03–3.15 (m, 2 H, CH), 3.34 (t, *J* = 9.0 Hz, 1 H, CH_2), 3.43 (t, *J* = 8.9 Hz, 1 H, CH_2), 4.16–4.22 (m, 2 H, CH_2), 4.28 (t, *J* = 2.5 Hz, 1 H, CH), 4.40 (t, *J* = 2.5 Hz, 1 H, CH), 4.70 (d, *J* = 2.0 Hz, 1 H, CH), 4.73 (d, *J* = 2.0 Hz, 1 H, CH), 4.98 (d, *J* = 1.5 Hz, 1 H, CH), 4.99 (d, *J* = 1.5 Hz, 1 H, CH), 7.16–7.22 (m, 12 H, ArH), 7.23–7.30 (m, 12 H, ArH), 7.58–7.62 (m, 8 H, ArH), 7.66–7.71 (m, 8 H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.3, 14.5, 19.0 (2C), 29.0, 29.2, 65.6, 66.0, 71.4, 71.5, 76.5, 76.8, 81.0, 84.2, 84.5, 84.8, 84.9, 85.7, 87.1, 98.6, 98.7, 126.4, 126.5, 128.2, 128.3, 129.4, 129.5, 135.5, 135.6, 171.1, 171.2; Infrared spectrum (thin film) cm^{-1}: 3061, 2961, 1602, 1502, 1370, 1185.

5. The enantiomeric purity of [(*S*)-COP-Cl]$_2$ is best determined after conversion to the acetylacetonate derivative. A mixture of [COP-Cl]$_2$ (15 mg, 0.010 mmol), sodium acetylacetonate (70 mg, 0.573 mmol), acetone (0.4 mL) and water (0.2 mL) is stirred vigorously at room temperature for 20 h. Methylene chloride (0.5 mL) and water (0.5 mL) are added, and the layers were separated. The aqueous layer is extracted with methylene chloride (0.5 mL x 3). The combined organic layers is dried ($MgSO_4$), filtered and concentrated to provide an orange residue. This residue is filtered through a short plug of silica gel (diameter = 0.25 cm, height = 4 cm) using 4% *i*-PrOH/hexanes as eluent. The enantiopurity of this sample was determined to be >99% by HPLC analysis (AD column, 95:5 hexane:*i*-PrOH, 230 nm); retention times were: 5.8 min for (*S*)-COP-acac and 3.8 min for (*R*)-COP-acac. The checkers found that a sample of (*S*)-COP-acac gave one signal at 5.1 min that was determined to be 97% pure by HPLC analysis (Diacel Chiralpak AD-H column (0.46 cm x 25 cm), 1 mg/mL sample concentration, flow rate of 1.0 mL/min, 95:5 hexanes: *i*-PrOH).

6. The enantiomer of [COP-OAc]$_2$ and [COP-Cl]$_2$ can be prepared in an analogous fashion from (η^5-(*R*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt prepared from (*R*)-valinol.[2]

7. Sodium hexafluoroacetylacetonate was purchased from Aldrich Chemical Company, Inc., and was used as received.

8. The checkers found that in one case it was necessary to stir the reaction for 11 h in order to achieve full conversion to the product. COP-hfacac prepared by this method was of sufficient purity to catalyze allylic imidate rearrangements in polar solvents such as tetrahydrofuran or methylene chloride. COP-hfacac can be purified further by filtration through a short plug of silica gel using methylene chloride as eluent. The checkers found that purification of a sample of (*S*)-COP-hfacac yielded an orange solid (89% yield after purification).

9. The product, hexafluoroacetylacetonate[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]palladium, displayed the following characterization data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.79 (d, J = 6.9 Hz, 3 H, CH_3) 0.83 (d, J = 7.0 Hz, 3 H, CH_3), 2.05–2.08 (m, 1 H, C*H*), 3.45 (td, J = 9.4, 5.1 Hz, 1 H, C*H*), 3.72 (t, J = 9.4 Hz, 1 H, CH_2), 4.33 (dd, J = 8.6, 5.3 Hz, 1 H, CH_2), 4.53 (t, J = 2.3 Hz, 1 H, C*H*), 4.90 (d, J = 2.3 Hz, 1 H, C*H*), 4.68 (d, J = 2.3 Hz, 1 H, C*H*), 5.95 (s, 1 H, C*H*), 7.19–7.29 (m, 12 H, Ar*H*), 7.54–7.56 (m, 8

H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 18.4, 29.3, 65.3, 72.3, 76.7, 78.9, 84.1, 84.8, 87.7, 90.1, 97.6, 116.5, 118.8, 126.5, 127.9, 128.9, 135.5, 173.3, 173.6, 174.1; Infrared spectrum (thin film) cm^{-1}: 3061, 2964, 1629, 1598, 1509, 1475, 1258, 1208, 1150.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This synthesis of (*S*)-COP-OAc dimer, is a modification of the procedure originally reported by Richards and Stevens.[3] The procedure has been streamlined and modified to enable large-scale preparation of this and related COP catalysts. Using the procedure detailed here and in the accompanying procedure,[2] 8.9 g [(*S*)-COP-OAc]$_2$ or 8.2 g of [(*S*)-COP-Cl]$_2$ can be made in 40% overall yield from sodium cyclopentadienide with only one chromatographic purification being required.

Palladation of (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt occurs in a diastereoselective fashion because of the large steric floor provided by the tetraphenylcyclobutadiene moiety. This floor forces the oxazoline into a single diastereomeric conformation, allowing *ortho*-palladation to proceed on only one of the diastereotopic positions of the cyclopentadienyl ring.[3]

[COP-OAc]$_2$ is a planar, chiral palladium(II) complex, which catalyzes the reaction of carboxylic acids with prochiral primary (*Z*)-allylic trichloroacetimidates to provide enantioenriched 3-acyloxy-1-alkenes.[4] These reactions proceed with predictable high stereoinduction and are accomplished at room temperature using low catalyst loadings. This acetate-bridged dimer serves also as a convenient precursor of enantiopure [COP-Cl]$_2$ and the enantiopure monomeric hexafluoroacetonylacetonate complex, COP-hfacac.

[COP-Cl]$_2$ is a planar chiral palladium(II) complex, which catalyzes the [3,3]-sigmatropic rearrangement of (*E*)-allylic trichloacetimidates to the corresponding trichloacetamides in high yields and enantioselectivities for a wide range of substituted trihaloacetimidates.[5] The use of [COP-Cl]$_2$ for the catalytic asymmetric rearrangement of allylic trihaloacetimidates is described in an *Organic Syntheses* procedure.[6] The corresponding hexafluoroacetylacetonate complex, COP-hfacac, also catalyzes asymmetric allylic trichloroacetimidate rearrangements.[7] It is more soluble than [COP-Cl]$_2$ and can be used in a wider variety of solvents. This enhanced solubility allows catalytic asymmetric allylic trichloroacetimidate rearrangements to be conducted at high substrate concentrations using as little as 1 mol % of COP-hfacac.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(η^5-(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt: Cobalt, [1,1',1'',1'''-(**η**4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]][(1,2,3,4,5-**η**)-1-[[[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,4-cyclopentadien-1-yl]-; (222400-02-4)

Palladium(II) acetate; (3375-31-3)

(*S*)-COP-OAc: Di-μ-Acetatobis[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-N)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium; (849592-74-1)

(*S*)-COP-Cl: Cobalt, bis[1,1',1'',1'''-(**η**4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]](di-**μ**-chlorodipalladium)bis[**μ**-[(1-**η**:1,2,3,4,5-**η**)-2-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl-**κ***N*3]-2,4-cyclopentadien-1-yl]]di-; (581093-92-7)

Sodium hexafluoroacetylacetonate: 2,4-Pentanedione, 1,1,1,5,5,5-hexafluoro-, ion(1-), sodium; (22466-49-5)

(*S*)-COP-hfacac: Hexafluoroacetylacetonate[(η^5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]palladium; (805315-08-6)

Larry Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971 where he is now Distinguished Professor of Chemistry. Professor Overman was Chair of the UC Irvine Department of Chemistry from 1990–1993.

Carolyn Anderson received her B.Sc. degree in Chemistry from the University of Michigan in 1998 and her Ph.D. in Chemistry from the University of California at Irvine (with Larry Overman) in 2003. She was a Dreyfus Postdoctoral Fellow at Pomona College (Claremont, California) under the mentorship of Daniel O'Leary (2004–2006). In 2006, she joined the faculty of Calvin College (Grand Rapids, Michigan) as an Assistant Professor of Chemistry. Her current research interests include using organometallic methods to synthesize libraries of strained carbocycles.

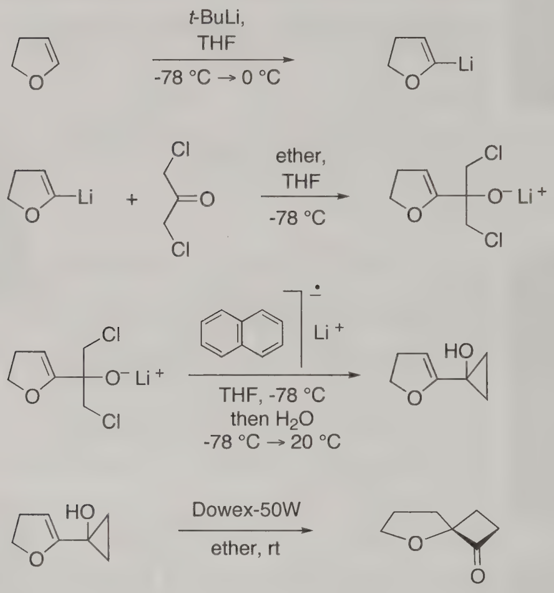
Chris Richards was born in Woking, England, and obtained a B.Sc degree in Chemistry from the University of Bath in 1989. This was followed by a Ph.D. in 1990 working with Professor Sue Gibson at the University of Warwick. After spending 1 year as an Alexander von Humboldt Research Fellow with Professor Helmchen at the University of Heidelberg, he took up a Lectureship at Cardiff University in Wales. In 2001 he moved to his current position of Reader at Queen Mary, University of London. His research interests encompass organometallic chemistry, organic synthesis, stereochemistry and catalysis.

Mary P. Watson received her B.A. from Harvard University in 2000, where she studied organic chemistry under the direction of Prof. David Evans. She then moved to University of California, Irvine, to work with Prof. Larry Overman. Her graduate research focused on the palladium(II)-catalyzed asymmetric allylic imidate rearrangement, including mechanistic studies performed in collaboration with Prof. Robert Bergman at the University of California, Berkeley. During her graduate work, she received the Allergan graduate student fellowship. She received her Ph.D. in 2006 and is currently a postdoctoral researcher at Harvard University with Prof. Eric Jacobsen.

Nicole S. White received her B.S. from the University of California, San Diego, in 2002. She then accepted a position in the medicinal chemistry department of Neurocrine Biosciences, where she worked on development of an MC4 antagonist aimed towards the treatment of cachexia. In 2004 she moved to the University of California, Irvine, to work with Prof. Larry Overman. Currently, her graduate research focuses on the use of palladium(II) catalysts to construct carbon–heteroatom bonds asymmetrically.

Brian S. Bodnar, born in 1981 in Trenton, NJ, obtained his B. S. degree from The College of New Jersey in Ewing, NJ, where he studied lithiation of benzamides under Dr. Lynn M. Bradley and analyzed microsatellite DNA of diatoms under Dr. James V. Bricker. After internships at Colgate-Palmolive Co. and Wyeth, he went to the University of Notre Dame in Notre Dame, IN to pursue a Ph. D. in organic chemistry under Dr. Marvin J. Miller. His research focuses on applications toward the synthesis of novel heterocyclic scaffolds and biologically useful molecules using acylnitroso hetero Diels-Alder chemistry.

1,3-DICHLOROACETONE AS A CYCLOPROPANONE EQUIVALENT: 5-OXASPIRO[3.4]OCTAN-1-ONE



Submitted by David G. Hilmey and Leo A. Paquette.[1a]
Checked by Richard Todd Bibart, Danny G. Lafrance and John A. Ragan.[1b]

1. Procedure

5-Oxaspiro[3.4]octan-1-one. Anhydrous tetrahydrofuran (100 mL) (Note 1) and 2,3-dihydrofuran (7.8 mL, 102 mmol, 1.3 equiv) (Note 2) are added to a single-necked 500-mL round-bottomed flask equipped with a rubber septum and previously purged with nitrogen. The magnetically stirred reaction mixture is cooled to –78 °C and 15 min later treated via cannula with *t*-butyllithium in pentane (1.7 M, 60 mL, 1.3 equiv) (Note 3) over 10 min. The resulting yellow solution is stirred in the cold for 30 min, at which point the acetone/dry ice bath is replaced by an ice-water bath and the reaction mixture is allowed to warm to 0 °C and kept at this temperature for 30 min (Note 4). Concurrently, dry ether (200 mL) and 1,3-

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dichloroacetone (10.0 g, 78.8 mmol, 1.0 equiv) (Note 5) are placed in a rubber septum-fitted 1-L flask and cooled to –78 °C under nitrogen with stirring (Note 6). The lithiated dihydrofuran solution is next introduced via cannula over 20 min (Note 7). After 2 h at –78 °C, a solution of lithium naphthalenide in tetrahydrofuran (197 mL of 1 M, 2.5 equiv) (Note 8) is introduced via cannula during 20 min to give a dark green solution that is stirred at –78°C for 4–5 h and at room temperature overnight (Note 9). The reaction mixture is then cooled to 0 °C and quenched with saturated aqueous sodium bicarbonate solution (250 mL). The separated aqueous phase is extracted with ether (3 x 100 mL) and the combined organic layers are dried over $MgSO_4$ and filtered. The solution that contains the crude, unstable cyclopropanol is charged with 10 g of Dowex-50W (Note 10) and a stir bar. The solution is stirred overnight. Solvent evaporation is performed with care on a rotary evaporator at 20 °C and 50 mmHg until solvent evaporation ceased. The residue is chromatographed on ~450 grams of silica gel with 5-25% ether in hexanes as eluent (Note 11). The fractions containing the product are carefully concentrated through rotary evaporation as previously described. 5-Oxaspiro[3.4]octan-1-one is obtained (6.9 g, 70%) as a faint yellow oil (Note 12).

2. Notes

1. Anhydrous tetrahydrofuran (fresh Sure-Seal bottle) and ether (fresh 500 mL bottle) were obtained from Aldrich and J. T. Baker, respectively, and used as provided.
2. 2,3-Dihydrofuran (99%+ purity) was obtained from Aldrich and used as provided.
3. *t*-Butyllithium was obtained from Aldrich and used as provided. An atmosphere of nitrogen was maintained in all vessels throughout the reaction.
4. A color change from yellow to almost colorless was witnessed during the warming process.
5. 1,3-Dichloroacetone of 95% purity was obtained from Aldrich and recrystallized from 1:3 ether/hexane, mp 43 °C.
6. 1,3-Dichloroacetone is soluble in ether at room temperature, but crystallizes from this medium at –78 °C. Accordingly, the addition of the lithiated 2,3-dihydrofuran was to a white suspension in ether.

7. The white solid dissolved during the addition leaving a yellow solution. If the solution went turbid again before the addition of lithiated 2,3-dihydrofuran was completed, the product yield was significantly decreased. The use of a fresh bottle of *t*-butyllithium proved to be quite helpful in eliminating appearance of turbidity and ensuring good conversion to product.

8. Lithium naphthalenide was prepared as follows: To an oven-dried, 500-mL, one-necked, round-bottomed, septum-stoppered flask was added dry tetrahydrofuran (200 mL), naphthalene (25.3 g, 197 mmol), and a teflon-covered stir bar. The flask was purged with argon. To the resulting solution was added lithium wire (1.37 g, 197 mmol containing 0.6-0.8% sodium) in small chunks (3–5 mm long) that had previously been scraped under oil and rinsed in hexanes to remove the oxide coating. The mixture, which developed a deep-green color during 30 min, was allowed to stir overnight and was considered to constitute a 1 M solution.

9. The progress of the reaction was monitored by TLC on glass-backed plates. 1,3-Dichloroacetone was not visible by UV or *p*-anisaldehyde staining. However, the product, which had an R_f value of 0.38 in 3:1 hexanes/ether, stained faintly under these conditions.

10. The ion exchange resin of 100 or 400 mesh was washed in turn with 150 mL of 5% HCl, 100 mL of water, 300 mL of methanol, and 500 mL of ether, then dried overnight under high vacuum (0.1 mmHg) to give dried Dowex resin.

11. When solvent evaporation slowed, the solid that resulted was taken up in toluene (25 mL) and the residual liquid was loaded onto a column of silica gel. With 5% ether in petroleum ether as the eluent, naphthalene eluted in fractions 4-6 (each of 200 mL volume). The desired cyclobutanone eluted in fractions 9-19 following an increase in solvent polarity to 25% ether in hexanes. The purity of the product was quite acceptable at this stage. Attempts at distillation led to decomposition.

12. The analytical properties of the volatile title compound were as follows: R_f = 0.38 in 25% ether in hexanes; IR (neat, cm^{-1}) 2954 (s), 2876(s), 1788 (s), 1058 (s), 1021(s); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.87–1.95 (m, 3 H), 2.01–2.17 (m, 3 H), 2.60–2.77 (m, 2 H), 3.87 (t, *J* = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 26.8, 33.9, 39.8, 70.2, 97.0, 211.9; MS (EI) *m/z* 127.06 $(M + H)^+$ calcd 144.05; Anal. Calcd. for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.24; H, 8.35.

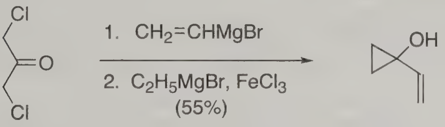
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

As a consequence of its highly reactive nature, cyclopropanone cannot conveniently be generated in preparative quantities in a laboratory setting.[2,3] Rather, the handling of this energetic compound has most often been made possible by virtue of its ability to undergo conversion to addition products from which the three-membered cyclic ketone may be released under relatively mild conditions. These precursors include the ethyl hemiketal,[4] 1-acetoxycyclopropanol,[5] and select carbinolamines.[6]

With the advent of 1,3-dichloroacetone as an article of commerce, an alternative cyclopropanone equivalent became available, although it has been little recognized as such. Several decades ago, the capacity of the halogenated acyclic ketone to undergo 1,2-addition reactions with Grignard reagents such as vinylmagnesium bromide was recognized.[7] The subsequent introduction of C_2H_5MgBr and a catalytic quantity of $FeCl_3$ delivered 1-vinylcyclopropanol in 55% yield. Barluenga's subsequent contribution was to recognize that the reductive cyclization of the initial Grignard adducts could be carried out as well with anhydrous $MgBr_2$ and lithium powder, or more conveniently with lithium naphthalenide in THF.[8] The second and third steps of the present procedure constitute a modification of the latter protocol. The lithiation of 2,3-dihydrofuran is adapted from the literature,[9] while the final step has its foundation in the many oxonium ion-initiated pinacolic ring expansion reactions explored in this laboratory.[10]



The use of 1,3-dichloroacetone as a cyclpropanone equivalent leads exclusively to 1-substituted cyclopropanols. Consequently, competing processes open to the parent ketone such as decarbonylation,[11] ring opening,[12] polymerization,[5,13] and twofold addition to the carbonyl group[3] do not operate. Advantageously, the present methodology is considered to be scalable, the only limitation being the need to remove naphthalene chromatographically. Finally, the chemistry here described is open to Grignard and organolithium reagents alike, and carries no restrictions as do cyclopropanone hemiacetals.[4]

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2,3-Dihydrofuran; (1191-99-7)
1,3-Dichloroacetone: 2-Propanone, 1,3-dichloro-; (534-07-6)
Lithium naphthalenide: Naphthalene, radical ion(1-), lithium; (7308-67-0)
5-Oxaspiro[3.4]octan-1-one; (881389-73-7)

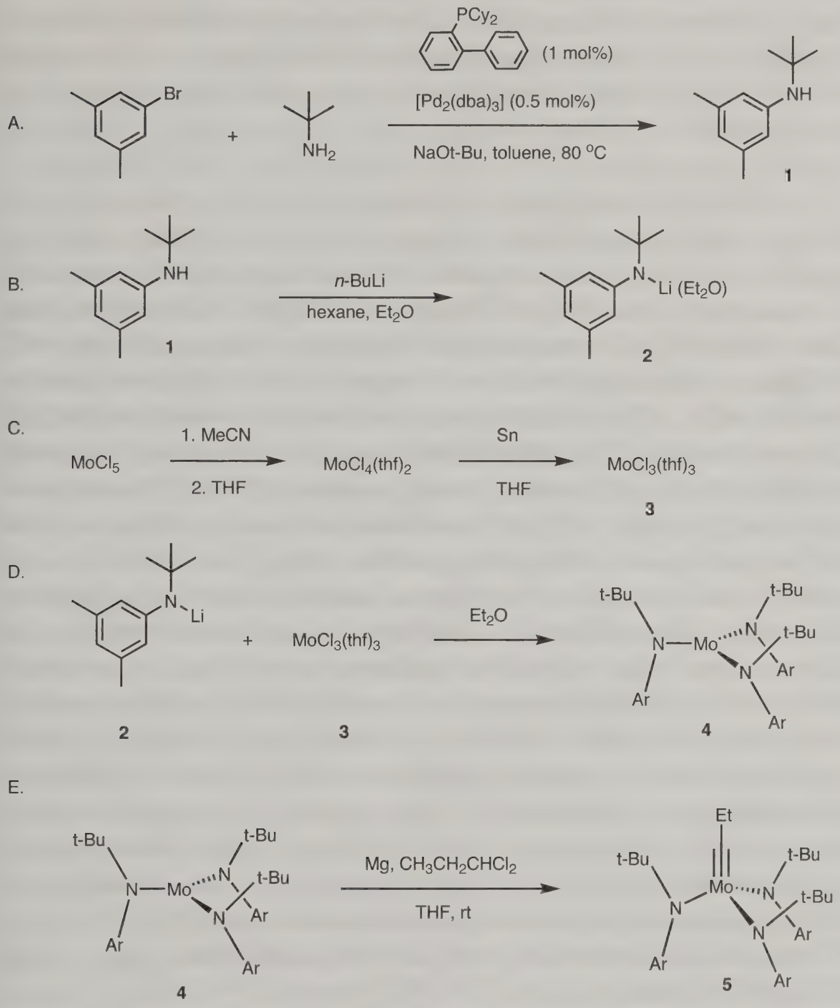
Leo Paquette was born in Worcester, Mass., obtained his B.S. degree in Chemistry from Holy Cross College in 1956, and was awarded the Ph.D. from M.I.T. in 1959 for his work on the synthesis of azasteroids with Norman Nelson. After 4 years as a medicinal chemist at the Upjohn Company, he joined the faculty at The Ohio State University where he quickly rose through the ranks to become Full Professor (1969-1981), Kimberly Professor (1981-1987), and University Distinguished Professor (1987-2003) prior to his retirement in 2004. Over the years, his research interests have spanned an enormous range from heterocyclic and hydrocarbon chemistry to the total synthesis of natural and unnatural products, the development of synthetic methodology and catalytic asymmetric methods, as well as chemistry based on organometallic and organosulfur reagents.

David Hilmey was born in Buffalo, NY in 1979. He received his B.S. in Medicinal Chemistry in 2001 from the State University of New York at Buffalo where he also conducted research on core-modified porphyrins under Professor Michael Detty. He then moved to The Ohio State University and obtained his Ph.D in 2006 under Professor Leo Paquette with research focused on heteroatom substituted spirocyclic scaffolds. He is currently a postdoctoral associate in the lab of Professor Tadhg Begley at Cornell University working on the chemical elucidation of thiamin biosynthesis.

Richard Todd Bibart was born in 1967 in Newark, Ohio. He received his B.A. in 1989 in chemistry from Wittenberg University, Springfield, Ohio, under the guidance of Nelson Sartoris. He received his Ph.D. from Stanford University in 1996 working with Dale Drueckhammer on the synthesis of Coenzyme A Analogs. After completion of his postdoctoral research with Leo Paquette in 1998, he joined the Regulatory and Analytical Sciences group at Merck and Co., Inc. He joined Pfizer in 2001 as a member of Analytical Research and Development.

Danny Lafrance was born in 1974 in Trois-Rivieres, Quebec, Canada. He received a B.Sc. degree in chemistry in 1996 from Laval University. He completed his M.Sc. at McGill University (Montreal, Canada) under the supervision of Professor Bruce A. Arndtsen, working on the insertion of imines and carbon monoxide into manganese-alkyl bonds. He then joined the process chemistry group of Schering-Plough, in New Jersey, where he worked for two years, before leaving for Montreal where he joined the Shire Biochem process chemistry group in 2001. He joined Pfizer in 2003 where he is working now in the Chemical Research and Development group.

PREPARATION OF A TRISAMIDOMOLYBDENUM(VI) PROPYLIDYNE COMPLEX – A HIGHLY ACTIVE CATALYST PRECURSOR FOR ALKYNE METATHESIS



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1. Procedure

CAUTION: Procedures involving molybdenum trisamide ***4*** *were conducted under an atmosphere of argon. It has been reported that* ***4*** *is able to activate molecular nitrogen at or below room temperature.*[2] *Therefore,* N_2 *must not be used as a protecting atmosphere for any experiment involving this reagent (Note 1).*

A. *N-(3,5-Dimethylphenyl)-tert-butylamine* ***(1)***. A 500-mL, three-necked, round-bottomed flask is equipped with two glass stoppers, a magnetic stir bar and a reflux condenser fitted with a gas inlet connected to an argon-vacuum manifold. The flask is flame-dried under vacuum, then filled with argon. After evacuating and backfilling with argon three times, the flask, in which a positive flow of argon is maintained throughout the entire procedure, is sequentially charged with sodium *tert*-butoxide (19.22 g, 0.20 mol) (Note 2), 2-(dicyclohexylphosphino)biphenyl (0.50 g, 1.4 mmol), $[Pd_2(dba)_3]$ (0.65 g, 0.71 mmol) (Note 3), toluene (200 mL) (Note 4), *tert*-butylamine (18.0 mL, 0.17 mol) and 5-bromo-1,3-dimethylbenzene (19.4 mL, 0.14 mol) (Note 2). The resulting viscous red reaction mixture is heated at 80 °C in an oil bath for 12 h while maintaining positive argon pressure. The solution color changes from dark red to orange red with white solids precipitating out. The mixture is transferred to a 500-mL, one-necked, round-bottomed flask and concentrated to a residue by rotary evaporation (water bath temperature 50–55 °C) before cooling down to room temperature (Note 5). *tert*-Butyl methyl ether (250 mL) (Note 2) and brine (80 mL) are added to the residue. After separation, the aqueous layer is extracted with *tert*-butyl methyl ether (2 x 250 mL), the combined organic layers are dried ($MgSO_4$), filtered and concentrated by rotary evaporation, and the crude product is purified by distillation under vacuum (bp 50–53 °C, 10^{-3} mbar, oil bath temperature 70 °C) affording aniline **1** as colorless liquid (21.8 g, 86%) (Note 6).

B. *Lithium N-(3,5-dimethylphenyl)-tert-butylamide etherate* ***(2)***. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers and a pressure-equalizing dropping funnel fitted with a gas inlet connected to an argon-vacuum manifold. The flask is flame-dried under vacuum, then filled with argon. After evacuating and backfilling with argon three times (Note 1), the flask is charged with substituted aniline **1** (11.3 g, 63.7 mmol) and *n*-hexane (220 mL) (Note 4) under argon purge. The solution is cooled to –78 °C in a dry ice-acetone bath and a solution of *n*-BuLi (1.6 M in hexanes, 48 mL, 76.8 mmol) (Note 2) is added via the dropping funnel over 10 min. After the addition is complete, the mixture is stirred for 12 h during which time it is gradually warmed to room temperature; a white precipitate forms upon warming. The dropping funnel is replaced by a distillation head and condenser and all volatiles are removed under vacuum (approximately 7.5 mmHg) at room temperature without exposing the contents to the open atmosphere (Notes 1, 7). Then ether (25 mL) and *n*-hexane (50 mL) (Note 4) are added to the remaining viscous liquid causing further precipitation of a white solid. The resulting suspension is kept at –30 °C under argon for 12 h (Note 1, 7). The white solids of lithium anilide etherate (**2**•Et_2O) formed are collected by filtration under argon, washed with cold *n*-hexane (2 x 10 mL) and dried under vacuum (10^{-3} mbar) to give lithium *N*-(3,5-dimethylphenyl)-*tert*-butylamide etherate as colorless crystals (9.41 g, 57%). The filtrate is concentrated under vacuum to approximately half of its volume and slowly cooled to −78 °C to give a second crop of the product which is isolated by filtration under argon as described above (3.48 g, 21%) (Note 8).

C. *[MoCl$_3$(THF)$_3$](**3**).* A 500-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, a glass stopper and a gas inlet connected to the argon/vacuum line is flame-dried and back-filled with argon. While maintaining a positive argon pressure, the flask is charged with acetonitrile (250 mL) (Note 4). Molybdenum pentacarbonyl ($MoCl_5$) (51.17 g, 160 mmol) is then added in portions over a period of 20 min, causing a gentle warming of the mixture. The resulting suspension is stirred for 20 h at ambient temperature. The solid material is filtered off and is carefully rinsed with acetonitrile (50 mL) before it is dried under vacuum (10^{-3} mbar) to give $MoCl_4(MeCN)_2$ as a red-brown solid (47.5 g, 93%). This material is re-dispersed in THF (200 mL) and the suspension is stirred for 3.5 h under argon. The resulting complex is filtered off under argon, the solid is carefully washed with pentane (100 mL) and dried under vacuum (10^{-3} mbar) to give $MoCl_4(THF)_2$ as orange-brownish crystals (53.30 g, 94%).

A 500-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, a glass stopper and a gas inlet connected to the argon/vacuum line is flame-dried and back-filled with argon. This flask is charged with the $MoCl_4(THF)_2$ complex (53.30 g, 140 mmol), THF (300 mL) and tin shot

(107.3 g, 0.904 mol), and the resulting suspension is stirred for 30 min, resulting in a slight exotherm (a temperature of approximately 30 °C is reached). Stirring is then discontinued to allow the remaining tin to settle. Upon gentle manual swirling, leaving the metallic tin at the bottom of the flask, the supernatant suspension (liquid and all solids except metallic tin) is decanted, the solid material is collected by filtration under argon, the product is carefully rinsed with pentane (100 mL) and dried under vacuum (10^{-3} mbar), affording $MoCl_3(THF)_3$ as an orange solid (51.2 g, 88%) (Note 9).

D. *Tris[N-(tert-butyl)(3,5-dimethylphenyl)-amido]molybdenum(III) (4).* A 500-mL two-necked, round-bottomed flask equipped with a magnetic stir bar, a glass stopper and a gas inlet connected to the argon/vacuum manifold is flame-dried under vacuum and back-filled with argon (Note 1). The flask is then charged with $[MoCl_3(THF)_3]$ **3** (7.96 g, 19.0 mmol) by removing a stopper and adding the solid, followed by Et_2O (300 mL) (Note 4), which is transferred by syringe. The resulting suspension is cooled to –30 °C with an acetone/dry ice bath before anilide **2** (9.79 g, 38.0 mmol) is added through removal of the stopper. The resulting mixture is stirred for 3 h during which time it is allowed to reach room temperature and the solution turns dark red. The suspension is filtered under argon into a flame-dried 500-mL, two-necked, round-bottomed flask to remove LiCl; the solid is rinsed with ether (15 mL). With one neck equipped with a rubber septum and the other one connected via a cold-trap to the vacuum line, the filtrate is concentrated under reduced pressure (7.5 mmHg) to approximately 1/6 of its original volume (50 mL) (Note 10). The remaining solution is cooled to – 30 °C for 16 h, causing the separation of dark red crystals. The supernatant liquid is decanted off while keeping a positive argon pressure, and the remaining dark-red, crystalline molybdenum trisamide **4** is dried under vacuum (10^{-3} mbar) (4.28 g, 55%) (Note 11).

E. *Tris[N-(tert-butyl)(3,5-dimethylphenyl)-amido]molybdenum(VI) propylidyne (5).* A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum, a magnetic stirring bar, and a gas inlet connected to the argon/vacuum manifold is flame-dried and back-filled with argon (Note 1, 10). Molybdenum trisamide **4** (5.31 g, 8.48 mmol), magnesium turnings (2.54 g, 106 mmol) (Note 2) and THF (160 mL) (Note 4) are added to the flask by removal of the septum. To the stirred solution, 1,1-dichloropropane (1.7 mL, 17 mmol) (Note 2, Note 12) is added dropwise via syringe within 5 min, resulting in a color change from red to dark amber. The resulting mixture is stirred for 2.5 h at room temperature under argon. The rubber septum is replaced by a distillation head connected to the vacuum line, the solvent is removed under reduced pressure (approximately 7.5 mmHg) (Note 10), and the residue is redissolved in pentane (100 mL) (Note 4). After vigorous stirring/manual shaking, the solid precipitate ($MgCl_2$) and excess magnesium turnings are removed by filtration under argon. The filtrate is concentrated to approximately 1/10 of its volume and slowly cooled to –78 °C, causing the molybdenum propylidyne complex to precipitate (Note 13). The supernatant is removed via cannula and the remaining beige crystals are dried under vacuum (10^{-3} mbar) (3.08 g, 54%) (Notes 1, 14, 15).

2. Notes

1. All compounds described in this procedure, except *N*-(3,5-dimethylphenyl)-*tert*-butylamine (**1**), are highly sensitive to air and moisture. Therefore, proper protection from atmospheric influences must be maintained throughout the preparation and handling of these products. The checkers ensured this by applying Schlenk techniques, whereas the submitters largely relied on the use of an argon-filled glove box.

2. Sodium *tert*-butoxide (97%), *tert*-butylamine (98%), 5-bromo-1,3-dimethylbenzene (97%), *tert*-butyl methyl ether (≥ 99%), *n*-butyllithium (1.6 M in hexanes), magnesium turnings (~3/16 in., 99.98%), 1,1-dichloropropane (97%, dried using activated, powdered 3Å molecular sieves overnight before use), *p*-nitrophenol (≥ 99%), 1-phenyl-1-butyne (99%, passed through a short plug of basic alumina and transferred under vacuum before use) were purchased from Aldrich Chemical Company, Inc. and used as received unless further purification indicated.

3. 2-(Dicyclohexylphosphino)biphenyl (98%), $[Pd_2(dba)_3]$, $MoCl_5$ (99.6%) and tin shot (99.8%) were purchased from Strem Chemicals, Inc. and used as received.

4. The checkers used solvents purchased from Acros which were purified and deoxygenated by distillation under argon over the drying agents indicated: toluene, hexane, pentane (Na/K alloy), Et_2O, THF, *tert*-butyl methyl ether (Mg-anthracene), MeCN (CaH_2). The submitters used toluene, hexane, Et_2O, THF and pentane deoxygenated by bubbling argon through them for a period of 20 min and dried using 3 Å molecular sieves overnight before use.

5. When cooling down to room temperature, the reaction mixture turned into a viscous solution, making the direct solvent removal under

vacuum impractical. In case this happens, *tert*-butyl methyl ether (250 mL) and H_2O (100 mL) should be added, and the aqueous layer removed. The organic layer should be concentrated under vacuum and the residue subjected to further workup as described in the text.

6. The procedure for synthesizing aniline **1** follows that reported by Fürstner, et al.[3a] The spectral characteristics of compound **1** are as follows: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (s, 9 H) 2.22 (s, 6 H), 3.30 (s, 1 H), 6.38 (s, 2 H), 6.41 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.5, 30.1, 51.3, 115.4, 120.2, 138.3, 146.8. According to ^{1}H NMR and GC/MS, the product contains approximately 3% of 5-bromo-1,3-dimethylbenzene as an impurity that cannot be separated at this stage. The spectroscopic data of **1** are in agreement with those reported in the literature.[3a]

7. With identical results, the reaction can be set up in the glove box.

8. The procedure for synthesizing anilide **2** follows that reported by Fürstner.[3a] The spectral characteristics of compound **2** are as follows: ^{1}H NMR (300 MHz, d_8-toluene) δ: 0.91 (t, J = 6.8 Hz, 6 H), 1.57 (s, 9 H), 2.29 (s, 6 H), 3.13 (q, J = 6.8 Hz, 4 H), 6.11 (s, 1 H), 6.52 (s, 2 H). These data are in agreement with those reported in the literature.[3a]

9. $MoCl_3(THF)_3$ prepared according to this procedure shows the following analytical properties: Elemental analysis calcd. for $C_{12}H_{24}Cl_3MoO_3$ (418.62): C 34.43, H 5.78; found: C 34.54, H 5.59. The submitters reported a "one-pot" preparation of **3** following a procedure reported by Poli.[4] Under these conditions, however, the checkers got erratic results with the appearance of the samples obtained in different runs ranging in color from orange to brown to lilac; in none of the cases was the elemental analysis correct. Therefore, the stepwise procedure outlined in the text is highly recommended.

10. The submitters performed this procedure in a glove box. The vacuum source was obtained by connecting an oil pump and a liquid nitrogen cold trap to a gas inlet with a hose in the glove box. The flask can be refilled with argon by closing the vacuum line and punching the septum with a needle. During concentration under vacuum, the flask was gently heated with a heat gun occasionally to speed the evaporation.

11. The procedure for synthesizing molybdenum triamide **4** follows that reported by Fürstner.[3a] The spectral characteristics of compound **4** are as follows: ^{1}H NMR (300 MHz, d_8-toluene) δ: –50.4 (br. s, 3 H), –20 (br. s, 6 H), –9.3 (br. s, 18 H), 61.7 (br, 27 H). Trisamide **4** can be used as such as an

efficient alkyne metathesis precatalyst upon *in situ* activation with CH_2Cl_2 in toluene.[3a, 9, 10]

12. Trisamide **4** was treated with 2 equiv of 1,1-dichloropropane instead of higher equiv in order to minimize a side product that presumably arises from a Grignard reaction.

13. The title compound's spectral characteristics are as follows: ^{1}H NMR (300 MHz, C_6D_6) δ: 1.45 (br. s, 30 H), 2.12 (s, 18 H), 3.13–3.95 (m, 2 H), 6.05 (br. s, 6 H), 6.66 (s, 3 H); ^{13}C NMR (150 MHz, THF-d_8) δ: 14.3 (br), 21.7, 33.9 (br), 45.6 (br), 61.2 (br), 127.7 (br), 130.9 (br), 137.3, 151.6 (br), 303.2; MS (EI, vaporization temperature = 130 °C): *m/z* (%): 665 (76) [M^+], 610 (100), 552 (80), 490 (41), 432 (32), 391 (44), 375 (70), 335 (48), 306 (19); HRMS (EI) ($C_{39}H_{59}MoN_3$): calcd for ^{98}Mo: 667.3764, found 667.3761. The deuterated solvents used were dried and deoxygenated by distillation over potassium metal chips before use. The product contained small amounts (< 5 wt% based on ^{1}H NMR integration) of *N-tert*-butyl aniline **1**,[7] which could not be removed even upon repeated recrystallization from pentane. Therefore, the product was used for alkyne metathesis without any further purification.

14. The submitters report testing of the metathesis activity of catalyst precursor **5** as follows: In the glove box under an atmosphere of argon (Note 1), toluene-d_8 (0.7 mL) was added to a mixture of molybdenum(VI) propylidyne **5** (3.7 mg, 0.0056 mmol) and *p*-nitrophenol (2.3 mg, 0.017 mmol) (Note 2) in a sealable NMR tube (Note 16). The color of the resulting catalyst solution changed from yellow to dark red within 4 min of mixing (Note 17). Then 1-phenyl-1-butyne (**6**) (16.0 μL, 0.112 mmol) (Note 2) was added to the catalyst solution. After mixing well, the metathesis reaction was monitored in this sealed NMR tube at 20 °C. The ^{1}H NMR (d1 = 5 s) (Note 18) spectrum was recorded until the ratio of 3-hexyne to **6** was constant. The reaction reached equilibrium within 10 min with 46% conversion obtained under closed system conditions (Note 19).

15. The submitters reported isolation of the molybdenum propylidyne complex **5** (5.05 g, 89%) as a light yellow powder by simple evaporation of the pentane under vacuum in the glove box. The product can be further purified by recrystallization from pentanes as originally reported.[5] The submitters did not observe noticeable difference in the catalytic activity of the catalyst generated from **5** after recrystallization or from **5** without recrystallization.

16. J. Young valve NMR tube (Wilmad-Labglass, product No. 528-JY-8) was used.

17. A red precipitate was observed during mixing, which was presumably due to the low solubility of the generated species in toluene. In the case of chloroform, ethyl acetate or THF as solvent, no precipitation was observed.

18. A long relaxation time (d1 = 5 s) was employed to ensure the accurate ^{1}H NMR integration on the signals of both starting compound **6** and products.

19. Ferrocene was used as internal standard and the mass balance was higher than 95%. Conversion was calculated from the integrated intensities of product and starting material. The equilibrium position was established by conducting the metathesis reaction in both forward (starting from **6**) and backward (starting from 3-hexyne and diphenylacetylene) directions. In both cases, the same molar ratio (1.0:1.7) of dimer to monomer was obtained.

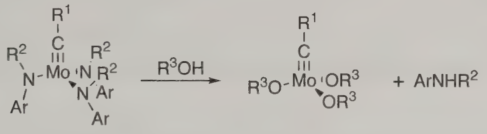
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

1. Discussion

Alkyne metathesis has attracted great interest in the past two decades due to its powerful application in both organic synthesis and polymer chemistry.[9] Ring closing alkyne metathesis (RCAM) has been successfully applied to natural products synthesis,[10] and acyclic diyne metathesis (ADIMET) has been employed in preparation of high molecular weight polymers.[11] More recently, one-step gram-scale synthesis of shape-persistent arylene ethynylene macrocycles from simple monomer precursors have also been accomplished.[8]

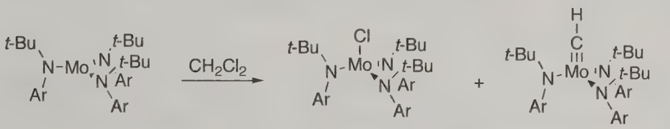
The application of alkyne metathesis depends on the availability and performance of the alkyne metathesis catalysts, especially with regard to convenience of catalyst synthesis, substrate compatibility, and temperature required for catalytic activity. The most readily available of these catalysts is a poorly characterized species.[12] Many of the known catalysts require high temperature (≥ 130 °C) for metathesis activity, and exhibit limited functional group tolerance. The first well-defined alkyne metathesis catalyst was the tungsten alkylidyne complex $(t\text{-BuO})_3\text{W}{\equiv}\text{C}(t\text{-Bu})$ developed by Schrock in the early 1980's.[13] Recently, Cummins has reported a new route to synthesize analogous trialkoxymolybdenum(VI) alkylidyne complexes $(\text{R}^3\text{O})_3\text{Mo}{\equiv}\text{CR}^1$, which are active alkyne metathesis catalysts even at room temperature.[14] Although trialkoxy alkylidyne **8** can be conveniently obtained from alcoholysis of the metathesis inactive triamide **7** (eq 1), the starting complex **7** [15] requires a time-consuming, multistep synthetic procedure and presents a practical limitation to this potentially useful catalyst.



(eq 1)

7 **8**

A related alkyne metathesis catalyst was developed by Fürstner who combined molybdenum trisamide **4** with methylene chloride to produce a mixture of $\text{ClMo[N}(t\text{-Bu})\text{Ar]}_3$ (**9**) and $\text{HC}{\equiv}\text{Mo[N}(t\text{-Bu})\text{Ar]}_3$ (**10**) (eq 2). This mixture exhibited alkyne metathesis activity at 80 °C with good functional group compatibility.[3a,b] The catalytically active species is derived from monochloride **9**, whereas methylidyne **10** exhibits poor metathesis activity.[16]

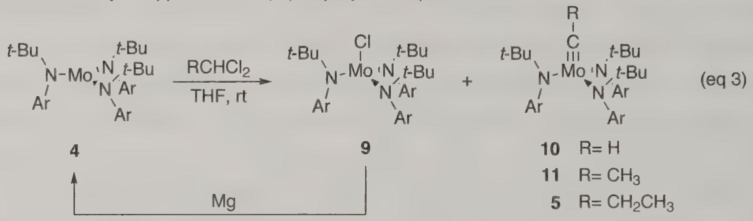


(eq 2)

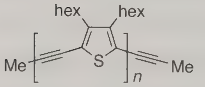
4 **9** **10**

Given that Fürstner's method directly produces alkylidyne **10**, which is the precursor to Cummins' active trialkoxyalkylidyne **8**, an expedient synthesis of complex **7** is envisioned to involve redirecting the reaction in eq 2 to favor production of $\text{HC}{\equiv}\text{Mo[N}(t\text{-Bu})\text{Ar]}_3$. Magnesium selectively reacts with monochloride **9** returning it to starting complex **4**, while complex **10** remains unaffected. In the presence of excess methylene chloride, the net result is a reductive recycle approach to selectively generate the desired complex **10** in one pot (eq 3).

Reductive recycle appoach to Mo(VI) alkylidyne complexes.



Using this method, trisamidomolybdenum(VI) ethylidyne **11** and –propylidyne **5** were prepared in high yield by the treatment of trisamide **4** with 1,1-dichloroethane or 1,1-dichloropropane, respectively, in the presence of magnesium. Treatment of trisamidomolybdenum(VI) propylidyne (**5**) – the catalyst precursor – with various phenols/alcohols produced alkyne metathesis catalysts active at room temperature. The Mo(VI) catalyst with *p*-nitrophenol as the ligand showed the highest catalytic activity.[17] In contrast to the reported incompatibilities of the tungsten alkylidyne complex ($(t\text{-BuO})_3W{\equiv}C(t\text{-Bu})$) with amines or polyether chains,[3a,10] the molybdenum(VI) propylidyne catalyst prepared through the reductive recycle strategy displayed good compatibility with these and other functional groups, as well as a wide variety of solvents.[17] This catalyst has been successfully used in synthesis of small molecules,[17] defect-free poly(thienyleneethynylene)s (PTEs) (**12**) and poly(phenyleneethynylene)s PPEs (**13**) with high molecular weight.[18] A variety of arylene ethynylene macrocycles (**14**, **15**) have also been successfully prepared in one step starting from monomers catalyzed by this Mo(VI) propylidyne catalyst.[8,19]



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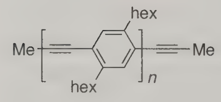

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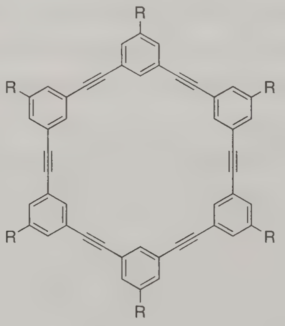

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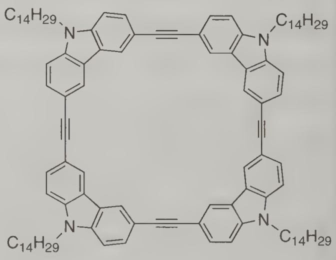
R = t-Bu, OTg, CH₂OTg, CO₂Tg, CO₂t-Bu

Tg = -(CH₂CH₂O)₃CH₃



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1. Roger Adams Laboratory, Departments of Chemistry and Materials Science & Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA. E-mail: jsmoore@uiuc.edu.
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Sodium *tert*-butoxide: 2-Propanol, 2-methyl-, sodium salt; (865-48-5)

2-(Dicyclohexylphosphino)biphenyl: Phosphine, [1,1'-biphenyl]-2-yldicyclohexyl-; (247940-06-3)

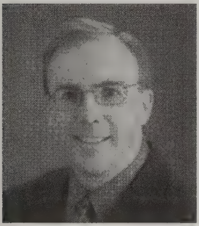
Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$]: Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-; (52409-22-0)

tert-Butylamine: 2-Propanamine, 2-methyl-; (75-64-9)

5-Bromo-*m*-xylene: Benzene, 1-bromo-3,5-dimethyl-; (556-96-7)

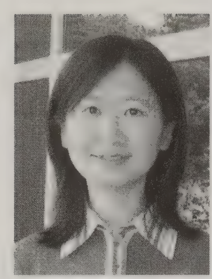
N-(3,5-Dimethylphenyl)-*tert*-butylamine: Benzenamine, *N*-(1,1-

dimethylethyl)-3,5-dimethyl-; (110993-40-3)
Butyllithium; (109-72-8)
Lithium *N*-(3,5-dimethylphenyl)-*tert*-butylamide etherate: Lithium, [*N*-(3,5-dimethylphenyl)tricyclo[3.3.1.13,7]decan-1-aminato][1,1'-oxybis[ethane]]-; (215180-13-5)
Molybdenum(V) chloride; (10241-05-1)
Tris[*N*-(*tert*-butyl)(3,5-dimethylphenyl)-amido]molybdenum(III): (236740-70-8)
1,1-Dichloropropane; (78-99-9)
Trisamidomolybdenum(VI) propylidyne: Molybdenum, tris[*N*-(1,1-dimethylethyl)-3,5-dimethylbenzenaminato]propylidyne-, (T-4)-; (616886-28-3)
p-Nitrophenol: 4-Nitrophenol; (100-02-7)
1-Phenyl-1-butyne: 1-Butynylbenzene; (622-76-4)



Jeffrey Moore was born near Joliet, IL in 1962. He received his BS in chemistry (1984) from the University of Illinois, and his PhD in Materials Science and Engineering with Samuel Stupp (1989). Following a NSF postdoctoral fellowship at Caltech with Robert Grubbs and an Assistant Professor appointment at the University of Michigan in Ann Arbor, he returned in 1993 to the University of Illinois, where he is currently the William H. and Janet G. Lycan Professor of Chemistry and Materials Science and Engineering. His research focuses on molecular self-assembly, structure-controlled macromolecules and foldamers, stimuli-responsive materials, and self-healing polymers

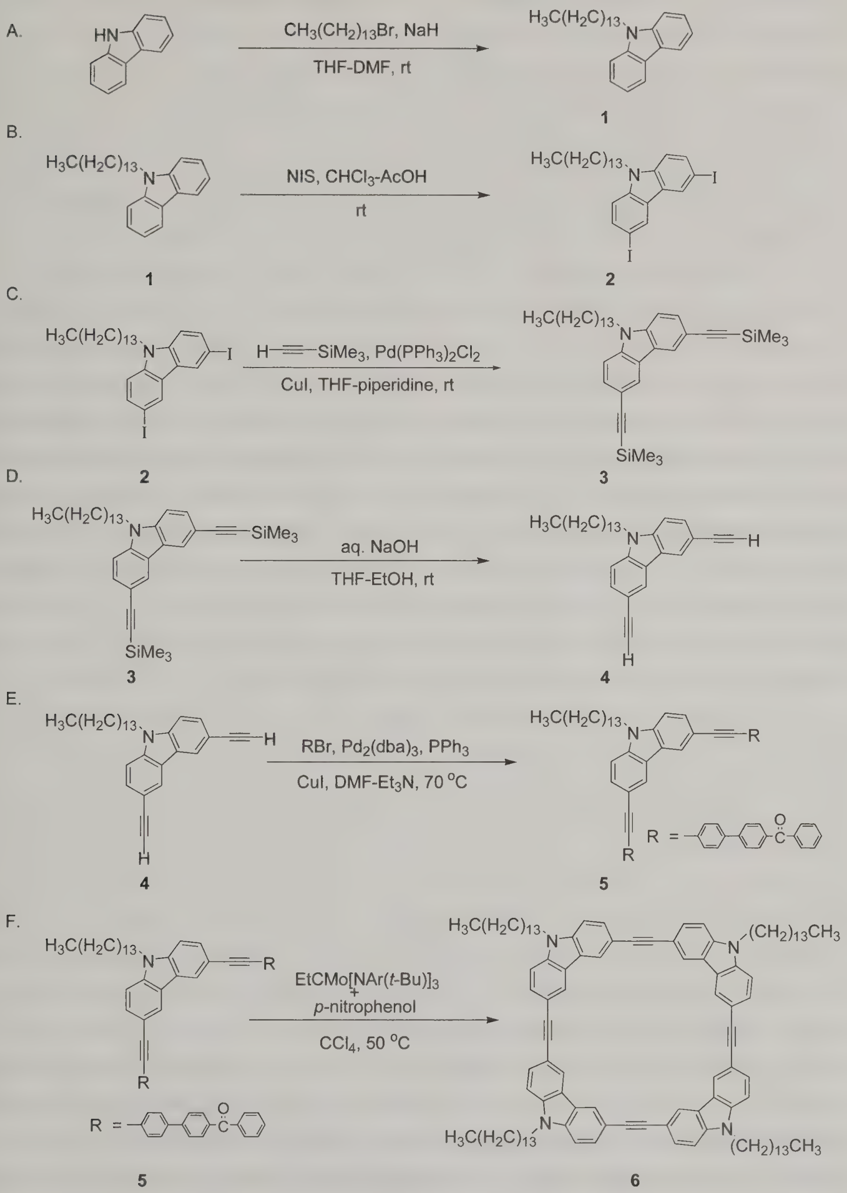
Wei Zhang was born in China in 1977. After completing his BS in chemistry in 2000 at Peking University and one year graduate study in University of Utah, he transferred to the University of Illinois at Urbana-Champaign in 2001, where he completed his PhD in chemistry with Prof. Jeffrey Moore, working on the development of molybdenum-based alkyne metathesis catalysts and their application to the synthesis of shape-persistent macrocycles and conjugated polymers (2005). In March 2006 he began a postdoctoral position at MIT with Prof. Timothy M. Swager.



Yunyi Lu was born in China in 1980. She received her BS in Chemistry from Nanjing University in 2003. In the same year, she began her graduate studies at the University of Illinois with Professor Jeffrey Moore. Currently she is working on the preparation and study of polymer nanofiltration membranes for water purification.

Günter Seidel (born 1947) studied Chemistry at the Fachhochschule Aachen Jülich to become an academically trained engineer. He is working at Max-Planck-Institute for Coal Research in Mülheim/Ruhr, Germany, since 1972. Until 1992 he worked on the preparation of recent organic boron compounds and their application in organic synthesis. Since 1993 he is working in Prof. Fürstner's group in the field of organometallic chemistry, C-C coupling reactions, transition-metal catalysts, and their application in the alkene- and alkyne metathesis. He is co-author of 83 publications and 1 patent.

PREPARATION OF A CARBAZOLE-BASED MACROCYCLE VIA PRECIPITATION-DRIVEN ALKYNE METATHESIS



Submitted by Wei Zhang, Hyeon Mo Cho and Jeffrey S. Moore.[1]
Checked by Scott E. Denmark and Christopher R. Butler.

Org. Synth. **2007**, *84*, 177-191
Published on the Web 11/16/06

1. Procedure

A. *9-Tetradecylcarbazole (1).* A single-necked 500-mL, round-bottomed, side-armed flask (Note 1) equipped with a glass stopper and a magnetic stirring bar is connected to a nitrogen-vacuum manifold. After evacuating and backfilling with nitrogen three times, the flask (with stopper removed), in which a positive flow of nitrogen is maintained throughout the entire procedure, is sequentially charged with carbazole (12.5 g, 0.072 mol) (Note 2), 1-bromotetradecane (24.3 mL, 0.079 mol) (Note 3), THF (60 mL) and DMF (20 mL) (Note 4). To the stirred solution, NaH (60% in oil, 4.32 g, 0.11 mol) (Note 3) is added to the solution in small portions within 20 min, avoiding vigorous bubbling and heating. The flask is capped with a glass stopper and the resulting suspension is stirred for 2 h at room temperature under nitrogen. Methanol (30 mL) is slowly added to the reaction mixture within 5 min to quench the remaining NaH. The solution is transferred to a 1-L, round-bottomed flask and then is concentrated by rotary evaporation (15–20 mmHg, water bath temperature 50–55 °C) to afford a solid residue, which is extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers are sequentially washed with 2 N aq HCl (2 x 100 mL), H_2O (2 x 100 mL), then are dried (Na_2SO_4) and concentrated by rotary evaporation. The crude product is purified by column chromatography [silica gel, 80 x 250 mm, hexanes] to afford carbazole **1** as a white solid (25.8 g, 98%) (Note 5).

B. *3,6-Diiodo-9-tetradecylcarbazole (2).* A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is sequentially charged with carbazole **1** (14.5 g, 0.040 mol), *N*-iodosuccinimide (19.1 g, 0.081 mol) (Note 6), $CHCl_3$ (280 mL) and acetic acid (100 mL). The flask is capped with a nitrogen inlet adapter and wrapped in aluminum foil. The reaction mixture is stirred under nitrogen for 16 h at room temperature. Chloroform and acetic acid are removed by rotary evaporation. A pink precipitate forms upon pouring water (450 mL) into the residue and then transferring the slurry into a 1-L Erlenmeyer flask containing more water (200 mL). The solids are collected by filtration, air dried and dissolved in $CHCl_3$ (300 mL). The organic solution is sequentially washed with saturated $Na_2S_2O_3$ (3 x 70 mL), brine (2 x 100 mL), dried (Na_2SO_4), filtered and concentrated by rotary evaporation (15–20 mmHg, water bath temperature 30–35 °C). Iodinated carbazole **2** is obtained as a white solid (23.8 g, 97%) and used without further purification (Note 7).

C. *3,6-Bis[(trimethylsilyl)ethynyl]-9-tetradecylcarbazole (3).* A 500-mL single-necked round-bottomed, side-arm flask equipped with a glass stopper and a magnetic stirring bar is connected to a nitrogen-vacuum manifold. After evacuating and backfilling with nitrogen three times, the flask, in which a positive flow of nitrogen is maintained throughout the procedure, is sequentially charged with iodinated carbazole **2** (23.7 g, 0.038 mol), CuI (0.147 g, 0.77 mmol) (Note 3), $Pd(PPh_3)_2Cl_2$ (1.35 g, 1.9 mmol) (Note 3), THF (90 mL), and piperidine (55 mL) (Note 3). The flask is cooled in an ambient temperature water bath before 1-trimethylsilylacetylene (45.7 mL, 0.38 mol) (Note 8) is added in two portions over 5 min (Note 9). The reaction mixture is then stirred for 23 h at room temperature. The solution changes from green to yellow with the formation of a white precipitate, and then the suspension changes to green and then black. The reaction mixture is then filtered through a coarse fritted funnel into a 1-L, one-necked, round-bottomed flask and is concentrated by rotary evaporation (15–20 mmHg, water bath temperature 40–45 °C). The crude product is purified by column chromatography [silica gel, 80 x 250 mm, hexanes 1 L, then hexanes/EtOAc 50/1 (2 L), then hexanes/EtOAc, 20/1 (1 L)] to afford diyne-substituted carbazole **3** as a yellow oil (19.9 g, 93%) (Note 10).

D. *3,6-Diethynyl-9-tetradecylcarbazole (4).* A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar is sequentially charged with diyne substituted carbazole **3** (19.5 g, 0.035 mol), THF (100 mL) and ethanol (400 mL). As the resulting solution is stirred, a solution of NaOH (4.21 g, 0.11 mol) in H_2O (30 mL) is added slowly over 5 min. The solution is stirred under nitrogen at room temperature for an additional 2 h during which time the solution changes from orange to red. The solvent is removed by rotary evaporation (water bath temperature 45–50 °C) to afford a residue, which is partitioned between CH_2Cl_2 (450 mL) and H_2O (100 mL) in a 1-L separatory funnel. The separated organic layer is washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), and then is dried (Na_2SO_4), filtered and concentrated by rotary evaporation (20–25 mmHg, water bath temperature 30–35 °C). Diyne-substituted carbazole **4** is obtained as a yellow-red oil that becomes a tan solid upon standing (14.0 g, 97%) and is used without further purification (Notes 11, 12).

E. *3,6-Bis(benzoylbiphenyl)ethynyl-9-tetradecylcarbazole (5).* A 500-mL, single-necked round-bottomed, side-arm flask equipped with a Teflon thermometer adapter and a magnetic stirring bar is connected to a nitrogen-vacuum manifold. The flask is flame-dried under vacuum, then filled with nitrogen. After evacuating and backfilling with nitrogen three times, the flask, in which a positive flow of nitrogen is maintained throughout the entire procedure, is sequentially charged with CuI (0.058 g, 0.31 mmol) (Note 3), $Pd_2(dba)_3$ (1.68 g, 1.8 mmol) (Note 13), PPh_3 (3.21 g, 12 mmol) (Note 13) and 4-benzoyl-4'-bromobiphenyl (21.7 g, 0.064 mol) (Note 14). The flask containing the solid mixture is evacuated and backfilled with nitrogen three times. Under a nitrogen purge, triethylamine (70 mL) (Note 3, Note 4) and a solution of diyne-substituted carbazole **4** (12.6 g, 0.031 mol) in DMF (150 mL) (Note 4) are sequentially added. Oxygen is removed from the mixture by three freeze-pump-thaw cycles. The reaction mixture is then stirred for 16 h at 70 °C (internal temperature). The solution changes from yellow to a dark purple. When the reaction mixture cools to room temperature, yellow precipitates are observed. The mixture is transferred to a 1-L, single-necked, round-bottomed flask with the aid of dichloromethane washes (2 x 250 mL). Dichloromethane and Et_3N are removed by rotary evaporation (15–20 mmHg, water bath temperature 40–45 °C) and DMF is removed under high vacuum by using a short-path distillation apparatus (0.50–1.0 mmHg, air bath temperature 45–55 °C) (Note 15). Dichloromethane (400 mL) is added and the organic layer is washed with saturated aq. NH_4Cl solution (2 x 200 mL), brine (2 x 200 mL) and then was dried (Na_2SO_4) and filtered. Dichloromethane is removed by rotary evaporation and the residual solid is treated with methanol (200 mL), resulting in the formation of a yellow solid. The solid bisarylethynyl-substituted carbazole **5** is collected by filtration, then is washed with methanol (3 x 50 mL), dried in vacuo (26.9 g, 95%) and used without further purification (Notes 16, 17).

F. *Carbazole-based tetrakismacrocycle (**6**)*. A 400-mL Schlenk tube equipped with a magnetic stirring bar and a glass stopper is introduced to a glove box. The flask is sequentially charged with 4-nitrophenol (0.680 g, 4.89 mmol) (Note 3), trisamidomolybdenum(VI) propylidyne (1.09 g, 1.63 mmol) (Note 18) and CCl_4 (150 mL) (Note 4). The resulting solution is stirred for 4 min and the solution changes from light yellow to orange (Note 19). A solution of monomer **5** (15.1 g, 16.3 mmol) in CCl_4 (200 mL) (Notes 20, 21) is added to the stirred catalyst solution. The flask is sealed with grease and electrical tape and is removed from the glove box. The resulting mixture is stirred at 50 °C (Note 22) for 24 h during which time a light-yellow precipitate forms and the color of the reaction mixture changes from yellow to brown. The mixture is transferred to a 1-L Erlenmeyer flask, along with CH_2Cl_2 (200 mL). The solids are removed by suction filtration through a medium-porosity fritted-glass funnel and are washed with CH_2Cl_2 (2 x 50 mL). The filtrate is concentrated by rotary evaporation (20–25 mmHg, water bath temperature 40–45 °C). Methanol (200 mL) is added to the residue and the resulting suspension is filtered, washed with methanol (3 x 75 mL) and dried in vacuo. The crude product is further purified by silica gel column chromatography (Note 3) [silica gel, 44 x 572 mm, $CHCl_3/CH_2Cl_2$, 3/1 to 1/1] to afford macrocyclic product **6** as a pale-yellow solid (3.80 g, 61%) (Notes 23, 24).

2. Notes

1. All glassware was oven-dried at 140 °C overnight.

2. Carbazole (96%) was purchased from Acros and used as received.

3. 1-Bromotetradecane (97%), sodium hydride (60% dispersion in mineral oil), CuI (99.999%), $Pd(PPh_3)_2Cl_2$ (98%), piperidine (redistilled, 99.5+%), triethylamine (99.5%), *p*-nitrophenol (≥ 99%) and grade 62 silica gel with pore size of 150 Å were purchased from the Aldrich Chemical Company, Inc. and used as received unless further purification is indicated.

4. THF and DMF were dried by standing over 4 Å molecular sieves over night before use. Carbon tetrachloride was distilled over P_2O_5 and stored over 3 Å molecular sieves.

5. A small portion of compound **1** was further purified by recrystallization from ethanol to afford analytically pure material. The analytical data from compound **1** were as follows: mp 42–44 °C; TLC: $R_f = 0.22$ (hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (t, $J = 7.4$ Hz, 3 H), 1.23–1.40 (m, 22 H), 1.87 (tt, $J = 7.3$ and 7.3 Hz, 2 H), 4.30 (t, $J = 7.3$ Hz, 2 H), 7.22 (dt, $J = 7.8$ and 0.9 Hz, 2 H), 7.40–7.48 (m, 4 H), 8.10 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 27.3, 28.9, 29.3, 29.4, 29.47, 29.54, 29.57, 29.62, 29.64, 31.9, 43.0, 108.6, 118.6, 120.3, 122.8, 125.5, 140.4. IR (KBr): 3048, 2947, 2919, 2869, 2848, 2341, 2360, 1628, 1600, 1485, 1465, 1453, 1371, 1351, 1328, 1235, 1153, 1122 cm^{-1}; LRMS (EI): *m/z* 363.3, 180.1. Anal. Calcd for $C_{26}H_{37}NO$: C, 85.89; H, 10.26; N, 3.85. Found: C, 86.12; H, 10.66; N, 4.03. The spectroscopic data were in agreement with those previously reported.[2]

6. *N*-Iodosuccinimide (95%) was purchased from the Aldrich Chemical Company, Inc. and used as received.

7. The analytical data from compound **2** were as follows: mp 79–80 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (t, J = 7.1 Hz, 3 H), 1.22–1.30 (m, 22 H), 1.81 (tt, J = 7.1 and 7.1 Hz, 2 H), 4.21 (t, J = 7.4 Hz, 2 H), 7.16 (d, J = 8.6 Hz, 2 H), 7.70 (dd, J = 8.6 and 1.7 Hz, 2 H), 8.32 (d, J = 1.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 27.2, 28.8, 29.31, 29.35, 29.35, 29.42, 29.51, 29.56, 29.61, 29.63, 29.65, 31.9, 43.2, 81.6, 110.9, 124.0, 129.3, 134.5, 139.5; IR (KBr): 3062, 2921, 2847 1585, 1466, 1428, 1374, 1348, 1312, 1290, 1236, 1216, 1152, 1047, 1014 cm^{-1}; LRMS (EI): *m*/*z* 615.1, 431.9, 208.1. These spectroscopic data were in agreement with those previously reported.[2]

8. 1-Trimethylsilylacetylene (98+%) was purchased from GFS Chemicals and used as received.

9. Upon addition of 1-trimethylsilylacetylene, a significant exotherm (15 °C) was observed, and stirring became difficult as the piperidine hydroiodide was formed.

10. The analytical data from compound **3** were as follows: TLC R_f = 0.32 (*n*-hexane/EtOAc, 20/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.28 (s, 18 H), 0.87 (t, J = 7.1 Hz, 3 H), 1.22–1.31 (m, 22 H), 1.83 (p, J = 7.1 Hz, 2 H), 4.25 (t, J = 7.2 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.56 (dd, J = 8.5 and 1.6 Hz, 2 H), 8.19 (d, J = 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.15, 14.1, 22.7, 27.2, 28.9, 29.32, 29.34, 29.45, 29.51, 29.57, 29.61, 29.63, 29.65, 31.9, 43.3, 92.0, 106.3, 108.8, 113.7, 122.3, 124.7, 130.0, 140.5; IR (film): 2926, 2854, 2153, 1869, 1629, 1598, 1483, 1406, 1382, 1350, 1318, 1287, 1248, 1202, 1149, 1133, 1059 cm^{-1}; MS (EI): *m*/*z* 555.4, 372.1, 73.1. These spectroscopic data were in agreement with those previously reported.[2]

11. A small portion of compound **4** was further purified by column chromatography (*n*-hexanes/EtOAc, 100/1 to 20/1) to afford analytically pure material. The analytical data from compound **4** were as follows: TLC R_f = 0.29 (*n*-hexanes/EtOAc, 20/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.22–1.35 (m, 22 H), 1.84 (tt, J = 7.1 and 7.1 Hz, 2 H), 3.00 (s, 2 H), 4.25 (t, J = 7.3 Hz, 2 H), 7.32 (d, J = 8.6 Hz, 2 H), 7.60 (dd, J = 8.3, 1.5 Hz, 2 H), 8.21 (d, J = 1.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 27.2, 28.9, 29.30, 29.33, 29.43, 29.50, 29.56, 29.60, 29.62, 29.64, 31.9, 43.3, 75.4, 84.7, 108.9, 112.7, 122.2, 124.7, 130.1, 140.6; IR (film): 3279 (s), 2924 (s), 2849 (s), 2103 (s), 1630 (m), 1598 (s), 1483 (s), 1381 (m), 1349 (s), 1321 (w), 1290 (s), 1234 (m), 1153 (s), 1134 (m), 882 (s), 812 (s), 728 (w), 681 (m), 653 (s), 614 (s) cm^{-1}; LRMS (EI): *m*/*z* 411.3, 228.1, 75.0. Anal. Calcd for $C_{30}H_{37}N$: C, 87.54; H, 9.06; N, 3.40. Found: C, 87.38; H,

8.78; N, 3.63. These spectroscopic data were in agreement with those previously reported.[2]

12. The appearance of more than one ^{1}H NMR singlet around δ 3.1 ppm (terminal acetylene) indicated the presence of mono-desilylation side product. In this case, **4** was further purified by column chromatography [*n*-hexanes/EtOAc, 100/1 to 20/1, TLC $R_f = 0.29$ (*n*-hexanes/EtOAc, 20/1].

13. $Pd_2(dba)_3$ and PPh_3 (99%) were purchased from Strem Chemicals, Inc. and used as received.

14. 4-Benzoyl-4'-bromobiphenyl (99%) was purchased from Lancaster and used as received.

15. The submitters reported the use of a Kugelrohr short-path distillation apparatus (Cat. No. Z401137-1SET), which was purchased from Aldrich Chemical Company, Inc.

16. A small portion (500 mg) of compound **5** was further purified by recrystallization from hot isopropyl acetate (ca. 20 mL) to provide analytically pure material. The analytical data from compound **5** were as follows: mp 162–167 °C; TLC $R_f = 0.26$ (CH_2Cl_2/*n*-hexanes, 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (t, $J = 7.1$ Hz, 3 H, CH_3), 1.19–1.41 (m, 22 H, CH_2), 1.89 (tt, $J = 7.1, 7.1$ Hz, 2 H), 4.31 (t, $J = 7.3$ Hz, 2 H), 7.40 (d, $J = 8.4$ Hz, 2 H), 7.52 (m, 4 H), 7.61 (tt, $J = 7.5, 1.4$ Hz, 2 H), 7.66–7.71 (m, 10H), 7.74 (d, $J = 8.6$ Hz, 4 H), 7.85 (m, 4 H), 7.92 (d, $J = 8.4$ Hz, 4 H), 8.32 (d, $J = 1.4$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 27.2, 28.9, 29.3, 29.46, 29.51, 29.57, 29.61, 29.62, 29.64, 31.9, 43.4, 87.6, 92.0, 109.1, 113.7, 122.5, 123.8, 124.2, 126.8, 127.2, 128.3, 129.8, 130.0, 130.8, 132.1, 132.4, 136.4, 137.7, 139.2, 140.6, 144.4, 196.3; IR (KBr): 2924, 2851, 2201, 1648, 1600, 1522, 1481, 1384, 1317, 1277, 1150 cm^{-1}. LRMS (MALDI): *m/z* 923.94, 825.5, 809.5, 755.9, 740.8, 567.4, 551.4, 545.4. Anal. Calcd for $C_{68}H_{61}NO_2$: C, 88.38; H, 6.65; N, 1.52. Found: C, 88.06; H, 6.41; N, 1.70. These spectroscopic data were in agreement with those previously reported.[2]

17. The submitters found that the appearance of more than one ^{1}H NMR triplet around δ 4.3 ppm (α-methylene protons on the tetradecyl side chain) indicated the presence of unreacted starting material and/or mono-alkynylated product. In this case, **5** could be further purified by column chromatography [*n*-hexanes/CH_2Cl_2, 1/1 v/v, TLC $R_f = 0.26$ (CH_2Cl_2/*n*-hexane, 1/1)].

18. Gram-scale preparation of trisamidomolybdenum(VI) propylidyne is reported in the preceding *Organic Syntheses* report.

19. A red precipitate was observed during mixing, and was presumably due to the low solubility of the species generated in CCl_4. In the case of chloroform, ethyl acetate or THF as solvent, no precipitate was observed.

20. Only a portion of monomer **5** dissolved in CCl_4 at the start of the reaction. However, the poor solubility of **5** did not affect the macrocycle synthesis. As the metathesis reaction proceeded, monomer **5** dissolved and was transformed into soluble macrocycles.

21. In addition to CCl_4, 1,2,4-trichlorobenzene and toluene are alternative solvents for the macrocycle synthesis. The amount of aromatic impurities observed in the reaction (based on ^{1}H NMR analysis) conducted in CCl_4 was less than that observed in toluene.

22. In a previous report on the small-scale synthesis of macrocycle **6** via precipitation-driven alkyne metathesis,[2] the reaction was conducted at 30 °C. However, for gram-scale preparation, the low solubility of oligomeric intermediates dramatically increased the solution viscosity and made stirring difficult. Raising the reaction temperature from 30 °C to 50 °C greatly improved the intermediate solubility and allowed efficient stirring.

23. The crude product **6** (after methanol wash, before column separation) was obtained in 98% yield (6.13 g) and contained a small amount of aromatic impurities (mainly 4-benzoyl-4'-bromobiphenyl). Macrocycles of high purity were obtained after column chromatography. The analytical data from compound **6** were as follows: mp 222–224 °C; TLC; $R_f = 0.89$ ($CHCl_3/CH_2Cl_2$, 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (t, $J = 7.1$ Hz, 12 H), 1.20–1.45 (m, 88 H), 1.90 (tt, $J = 7.1, 7.1$, 8 H), 4.31 (t, $J = 7.1$ Hz, 8 H), 7.39 (d, $J = 8.5$ Hz, 8 H), 7.71 (dd, $J = 8.3, 1.3$ Hz, 8 H), 8.42 (d, $J = 0.7$ Hz, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 27.3, 29.0, 29.35, 29.50, 29.55, 29.60, 29.64, 29.67, 31.9, 43.3, 89.0, 108.9, 114.4, 122.6, 123.9, 129.3, 140.1; IR (KBr): 2922, 2848, 1628, 1599, 1570, 1490, 1382, 1352, 1307, 1283, 1214, 1148, 1131 cm^{-1}; MS (MALDI): *m/z* 1542.7, 1370.1. Anal. Calcd for $C_{112}H_{140}N_4$: C, 87.22; H, 9.15; N, 3.63; Found: C, 86.84; H, 9.19; N, 3.26. These spectroscopic data were in agreement with those previously reported.[2]

24. The checkers found that accurate analytical data could be obtained from **6** only after thorough drying at 0.3 mm Hg in an Abderhalden apparatus heated with refluxing xylenes.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

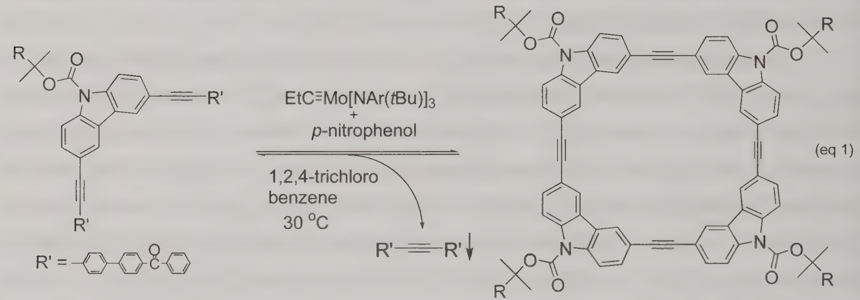
Shape-persistent arylene ethynylene macrocycles have attracted attention in the fields of supramolecular chemistry and materials science over the past decade due to their novel properties and potential applications.[3] However, the study and application of shape-persistent macrocycles are impeded by inefficient macrocycle syntheses. The usual preparation involves a large number of synthetic steps, requires dilute conditions (< 1 mM), and affords low overall yields.[4] Considerable efforts have been devoted to the development of methodologies allowing selectively functionalized structures to be obtained in high yields.

Conventional synthetic routes for arylene ethynylene macrocycles are dominated by Sonogashira coupling[5] between aryl iodides and terminal acetylenes and Glaser-type couplings[6] between terminal acetylenes. These cross-coupling approaches have advantages such as high tolerance of functional groups, with generally high yields in the individual steps. However, to obtain high yields of macrocycles, precursor oligomers must be pre-synthesized in a stepwise fashion and subsequently subjected to cross-coupling reactions under pseudo-high dilution condition (< 1 mM) to form macrocycles via intramolecular cyclization. Such tedious and time-consuming synthesis of the precursors impedes the efficient large-scale preparation of macrocycles via this route. Random cyclization of three or more monomer units has also been applied to preparing target macrocycles, but usually only low yields (1–18% on cyclization step) were obtained.[7]

Inspired by the successful applications of thermodynamically controlled reversible reactions in preparing unique molecular architectures[8] such as macrocyclic compounds, molecular capsules and interlocked structures, we envisioned that a convenient synthesis of arylene ethynylene macrocycles could be accomplished by using dynamic covalent chemistry.[9] In the past two decades, there has been rapid progress in alkyne metathesis catalyzed by either defined carbyne complexes[10] or catalysts generated in situ.[11] The ready availability of highly active Mo(VI) alkylidyne catalysts synthesized by a reductive recycle strategy[12] and successful examples of using dynamic covalent chemistry in organic syntheses prompted us to develop a synthetic approach to macrocycle preparation directly from a monomer.

We reported a successful approach involving precipitation-driven alkyne metathesis for convenient, multi-gram synthesis of arylene ethynylene macrocycles near room temperature.[2] Driven by the precipitation of a diarylacetylene byproduct, the desired macrocycles were obtained in one step from monomers in high yields. Macrocycle formation is a thermodynamically favored process under equilibrium control.[13]

We have utilized precipitation-driven alkyne metathesis to prepare other carbazole-based tetrameric macrocycles, such as **10c**. The four side chains are easily removed via thermolysis.[14] The resulting macrocycles may exhibit interesting electronic properties such as mixed-valence (MV) states.[15]



9a: R = Methyl
9b: R = Heptyl
9c: R = dodecyl

10a:	R = Methyl	< 5%
10b:	R = Heptyl	< 5%
10c:	R = dodecyl	81%

Three dialkyne monomers **9a-c**, which are functionalized with *t*-butyl carboxylate, 1,1-dimethyloctyl carboxylate and 1,1-dimethyltridecyl carboxylate, respectively, were prepared and subjected to standard metathesis conditions (eq 1). In the case of **9a-b**, at the end of the reaction nearly quantitative conversion of starting monomers into insoluble materials was observed. Based on elemental analysis, the insoluble materials are believed to be a mixture of intermediate oligomers and diarylacetylene byproduct. In great contrast, metathesis of monomer **9c** proceeded well in 1,2,4-trichlorobenzene at 30 °C, and tetrameric macrocycle **10c** was obtained in 81% isolated yield.[16]

The successful generation of tetrameric macrocycle **6** and **10c**, as well as those failed cases when using monomer **9a-b**, illustrate the importance of balancing the solubility through the course of macrocycle formation.[13] In the case of metathesis of **9a-b**, the generated oligomeric species, either open-chain or cyclic versions, presumably precipitate out of solution due to their insufficient solubility. In great contrast, carbazole oligomers with 1,1-dimethyltridecyl carboxylate side chains (from metathesis of **9c**) have better solubility and intermediate species remain in solution, thus allowing for high yield formation of tetracycles via alkyne metathesis—a dynamic covalent approach.

This finding has important practical significance in that it demonstrates that the solubility of longer arylene ethynylene oligomers, especially those overshooting the target macrocycle length, must be taken into consideration to accomplish high-yield macrocycle syntheses. All the intermediate compounds should be sufficiently soluble along the reaction pathway to allow the thermodynamically stable product to be obtained through reversible alkyne metathesis.

It is envisioned that the successful preparation of macrocycles using the precipitation-driven, reversible alkyne-metathesis may open the way to other two-dimensional or three-dimensional arylene ethynylene structures, as well as alkyne-bridged oligomers and polymers.

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16. The characterization data for macrocycle **10c** were as follows: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (t, *J* = 6.6 Hz, 12 H, $OC(CH_3)_2CH_2(CH_2)_{10}CH_3$], 1.23–1.54 (m, 80 H, $OC(CH_3)_2CH_2(CH_2)_{10}CH_3$], 1.80 [s, 24 H, $OC(CH_3)_2CH_2(CH_2)_{10}CH_3$], 2.11 [m, 8 H, $OC(CH_3)_2CH_2(CH_2)_{10}CH_3$], 7.44 (d, *J* = 8.6 Hz, 8 H), 8.00 (s, 8 H), 8.10 (d, *J* = 8.6 Hz, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1, 22.7, 24.2, 26.4, 29.4, 29.5, 29.6, 29.7 (br, signal overlap), 30.0, 31.9, 40.8, 87.0 [$OC(CH_3)_3$], 89.1 [ArCCAr], 116.0, 118.2, 122.4, 125.1, 130.7, 138.0, 150.5 (NCOO); MS (FD): m/z (%): 1773.3 (21), 887.0 (100), 525.3 (66); Anal. Calcd for $C_{120}H_{148}N_4O_8$ (1773.1): C, 81.22; H, 8.41; N, 3.16; Found: C, 80.93; H, 8.05; N, 3.24; GPC 2030 (M_n), 1.02 (M_w/M_n).

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Carbazole: 9H-Carbazole; (86-74-8)
1-Bromotetradecane; (112-71-0)
Sodium hydride; (7646-69-7)
N-Iodosuccinimide: 1-Iodo-2,5-Pyrrolidinedione; (516-12-1)
Copper(I) iodide; (7681-65-4)
Dichlorobis(triphenylphosphine)palladium(II); (13965-03-2)
Piperidine; (110-89-4)
1-Trimethylsilylacetylene: Silane, ethynyltrimethyl-; (1066-54-2)
Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$]; (52409-22-0)
Triphenylphosphine; (603-35-0)
4-Benzoyl-4’-bromobiphenyl: ethanone, (4'-bromo[1,1'-biphenyl]-4-yl)phenyl-; (63242-14-8)
Trisamidomolybdenum(VI) propylidyne: Molybdenum, tris[*N*-(1,1-

dimethylethyl)-3,5-dimethylbenzenaminato]propylidyne-, (T-4)-; (616886-28-3)

p-Nitrophenol: 4-Nitrophenol; (100-02-7)

9-Tetradecylcarbazole: 9-Tetradecyl-9*H*-carbazole; (20863-25-6)

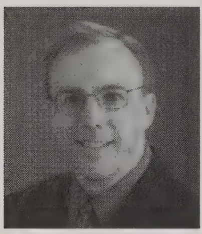
3,6-Diiodo-9-tetradecylcarbazole: 3,6-Diiodo-9-tetradecyl-9H-carbazole: (197860-64-3)

3,6-Bis[(trimethylsilyl)ethynyl]-9-tetradecylcarbazole: 9H-Carbazole, 9-tetradecyl-3,6-bis[(trimethylsilyl)ethynyl]- ; (197860-65-4)

3,6-Diethynyl-9-tetradecylcarbazole; (188740-71-8)

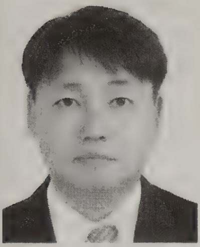
3,6-Bis(benzoylbiphenyl)ethynyl-9-tetradecylcarbazole: Methanone, [(9-tetradecyl-9H-carbazole-3,6-diyl)bis(2,1-ethynediyl[1,1'-biphenyl]-4',4-diyl)]bis[phenyl-; (791090-33-0)

Carbazole-based tetrakismacrocycle; (245648-36-6)



Jeffrey Moore was born near Joliet, IL in 1962. He received his BS in chemistry (1984) from the University of Illinois, and his PhD in Materials Science and Engineering with Samuel Stupp (1989). Following a NSF postdoctoral fellowship at Caltech with Robert Grubbs and an Assistant Professor appointment at the University of Michigan in Ann Arbor, he returned in 1993 to the University of Illinois, where he is currently the William H. and Janet G. Lycan Professor of Chemistry and Materials Science and Engineering. His research focuses on molecular self-assembly, structure-controlled macromolecules and foldamers, stimuli-responsive materials, and self-healing polymers.

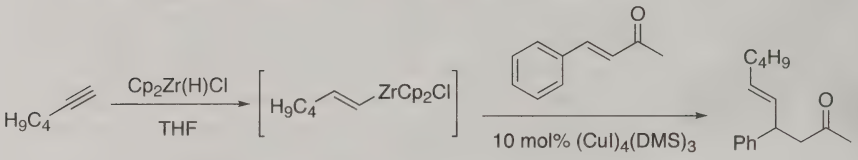
Wei Zhang was born in China in 1977. After completing his BS in chemistry in 2000 at Peking University and one year of graduate study at the University of Utah, he transferred to the University of Illinois at Urbana-Champaign in 2001, where he completed his PhD in chemistry with Prof. Jeffrey Moore, working on the development of molybdenum-based alkyne metathesis catalysts and their application to the synthesis of shape-persistent macrocycles and conjugated polymers (2005). In March 2006 he began a postdoctoral position at MIT with Prof. Timothy M. Swager.



Hyeon Mo Cho was born in South Korea in 1971. After receiving his BS in chemistry from Yonsei University (Seoul, 1994), he completed his MS (1997) and PhD (2002) in chemistry, also at Yonsei University, working on organosilicon compounds with Chang Hwan Kim and Myong Euy Lee. In 2002, he studied silica nanotube and siloxanes as a postdoctoral fellow at Natural Science Research Institute of Yonsei University. He then went to the University of Illinois as a postdoctoral fellow to study with Jeffrey Moore (2004). Currently he is a senior researcher at Electronic Chemical Materials R&D Center of Samsung Cheil Industries Inc.

Christopher Butler received a bachelor's degree in Chemistry from Illinois Wesleyan University in 2000. He then worked for three years in drug discovery at Johnson & Johnson Pharmaceutical Research & Development in San Diego, CA, before beginning graduate school at the University of Illinois working with Professor Scott E. Denmark in 2003. His thesis work focuses on the development of palladium-catalyzed vinylation of aryl and heteroaryl bromides using inexpensive polyvinylsiloxanes.

COPPER(I) IODIDE DIMETHYL SULFIDE CATALYZED ADDITION OF A VINYLZIRCONIUM REAGENT. PREPARATION OF 4-PHENYL-5(E)-DECEN-2-ONE



Submitted by Amer El-Batta and Mikael Bergdahl.[1]
Checked by Monica Trincado, Yazmin Rosa-Bauza, and Jonathan A. Ellman.

1. Procedure

An oven-dried 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum and a water condenser provided with an argon atmosphere inlet, is charged with Schwartz's reagent (9.36 g, 36.3 mmol) (Note 1) by temporarily removing the septum. The flask is immersed in an ice/water cooling bath equipped with an external thermometer (Note 2), and placed on a magnetic stir plate. Under an atmosphere of argon, 25.0 mL of tetrahydrofuran (Note 3) and 1-hexyne (3.71 mL, 33.0 mmol) (Note 4) are added to the flask by syringe through the septum. After stirring for 5 min, the ice/water cooling bath is replaced by an oil bath equipped with an external thermometer. Stirring is maintained and the reaction flask is heated to 40 °C for 6 h. The resulting yellow solution is cooled to room temperature (Note 5), *trans*-4-phenyl-3-buten-2-one (4.82 g, 33.0 mmol) is added (Note 6) and 5 min later copper(I) iodide-dimethyl sulfide complex (782 mg, 3.30 mmol) (Note 7) is added by temporarily removing the septum. The reaction temperature is increased to 40 °C, and the stirring is continued under an argon atmosphere for 12 h. The heating is interrupted and the oil bath is replaced by an ice/water bath. After removing the argon inlet and the water condenser, the reaction mixture is quenched with ether saturated with water (50 mL) at the ice/water bath temperature. The resulting heterogeneous mixture is stirred for 10 min and filtered in *vacuo* through a Celite® pad (Note 8) in a Büchner funnel. The Celite is carefully washed with 3 x 100 mL portions of ether, and the resulting ethereal phase is transferred to a 500-mL separatory funnel. The organic

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layer is washed with 2 x 20 mL of saturated sodium bicarbonate solution, dried over sodium sulfate (Note 9), filtered through a second Celite pad in a Büchner funnel, and concentrated under reduced pressure. The resulting crude product is purified on a silica gel 60Å chromatography column (38 cm x 4 cm) (Note 10) using a hexanes-ethyl acetate 1:0-10:1 gradient (Note 11) (Note 12). Removal of the eluent in *vacuo* afforded 5.55 g (24.1 mmol, 73%) of 4-phenyl-5(*E*)-decen-2-one as a light yellow oil (Note 13).

2. Notes

1. The submitters prepared bis(cyclopentadienyl)zirconium chloride hydride by lithium aluminum hydride reduction of bis(cyclopentadienyl)zirconium dichloride employing the procedure of Buchwald and his coworkers.[2] The checkers purchased Schwartz's reagent from Strem Chemicals, Inc. (Cat. No. 40-1040), and it was used as received.

2. The reaction has not been conducted on a larger scale than 36.3 mmol. As the reaction was mildly exothermic,[3] use of an ice/water bath is recommended on a larger scale.

3. Tetrahydrofuran was freshly distilled from sodium/benzophenone under an argon atmosphere (submitters) or dried through an alumina column (checkers).

4. 1-Hexyne was purchased from Aldrich Chemical Company, Inc. (Cat. No. 24,442-2) and was used as received. The alkyne was slowly added (~1 mL/min) using a gas tight syringe.

5. The flask was placed in a water bath and the mixture was stirred for 10 min.

6. Benzalacetone was purchased from Aldrich Chemical Company, Inc. (Cat. No. 24,109-1) and was used as received.

7. Copper(I) iodide (submitters used 98%, checkers used 99.999%), commercially available from Aldrich Chemical Company, Inc., was purified via its dimethyl sulfide complex following the House protocol.[4] Copper(I) iodide (5.0 g, 26 mmol) in 15 mL of anhydrous ether (ACS grade) was mixed with 20 mL (380 mmol) of dimethyl sulfide (Aldrich Chemical Company, Inc., Cat. No. 47,157-7). The resulting yellow solution was filtered through a cotton plug to remove heterogeneous material. The filtrate was diluted with 50 mL of cold hexanes. The crystalline material obtained was filtered with suction and washed with cold hexanes (3 x 50 mL) to afford 5.1 g of the copper complex as white prisms. The CuI/DMS complex

was subsequently dried under vacuum (ca. 0.1 mbar) at room temperature where it rapidly lost DMS and reached a constant weight within two hours to afford 4.5 of white crystals. Elemental analysis of this material indicated a stoichiometry of CuI/0.75 DMS. Anal. Calcd. for $C_6H_{18}Cu_4I_4S_3$: C, 7.60; H, 1.91; S, 10.15. Found: C, 7.53; H, 1.72; S, 10.13.

8. Celite 545® was purchased from Fisher Scientific Co. (Cat. No. C212-500).

9. Sodium sulfate was purchased from EMD Chemicals, Inc.. (Cat. No. SX0763-3).

10. Silica gel was purchased from Whatman (Cat. No. 4745-250), 230-400 Mesh.

11. Ethyl acetate and hexanes were purchased from Fisher Scientific, ACS reagent grade. The submitters applied flash-chromatography conditions with 10% ethyl acetate in hexanes.

12. The product had a TLC R_f value of 0.47 [ethyl acetate : hexanes, 1:10].

13. The submitters' reported a yield of 6.23 g (82%). Full characterization of the product was as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, *J* = 6.8 Hz, 3 H), 1.26–1.42 (m, 4 H), 2.03–2.09 (m, 2 H), 2.09 (s, 3 H), 2.85 (dd, *J* = 7.6, 7.2 Hz, 2 H), 3.91 (q, *J* = 7.2 Hz, 1 H), 5.53 (dtd, *J* = 15.2, 7.2, 0.8 Hz, 1 H), 5.62 (ddt, *J* = 15.2, 7.2, 1.2 Hz, 1 H), 7.20–7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9 (CH_3), 22.3 (CH_2), 30.6 (CH_3), 31.6 (CH_2), 32.3 (CH_2), 44.0 (CH), 49.8 (CH_2), 126.4 (CH), 127.5 (2xCH), 128.6 (2xCH), 130.9 (CH), 132.3 (CH), 143.8 (C), 207.0 (CO); IR (thin film) cm^{-1}: 1716, 1602, 1494, 1453, 968, 699; HRMS (EI) *m/z* Calcd for $C_{16}H_{22}O$: 230.1671. Found: 230.1671. The purity of the product was determined to be >98% by ^{1}H NMR and elemental analysis. Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.46; H, 9.72.

Safety and Waste Disposal Information

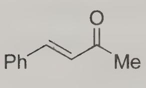
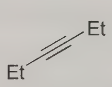
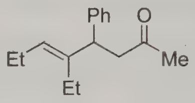
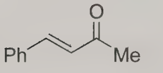
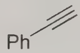
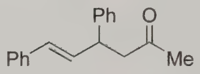
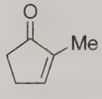
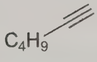
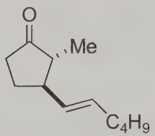
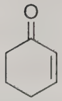
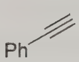
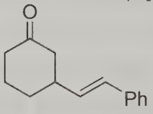
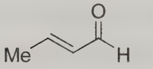
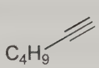
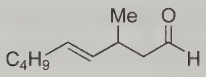
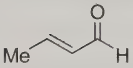
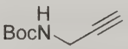
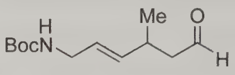
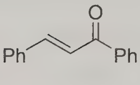
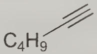
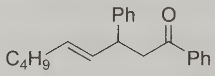
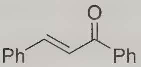
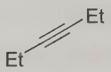
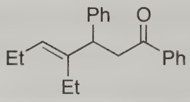
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The CuI•0.75DMS complex is an excellent catalyst for the direct conjugate addition of alkenyl groups from vinylzirconocene reagents to α,β-unsaturated aldehydes and ketones.[5] The presence of the catalyst with an alkenylzirconocene, at 40 °C in THF, circumvents the need for making discrete alkenylcopper reagents. The catalyst is superior in terms of product yields and alkene flexibility in comparison to other copper(I) sources as well as the nickel(II)[6] catalyzed conjugate addition. This simple one-pot procedure shows that one equivalent of the vinylzirconocene relative to the enone is needed to afford a high yield of the 1,4-addition of the alkenyl group. Some representative examples of the present reaction are shown in Table 1.

Copper(I) catalyzed conjugate additions of vinylzirconocenes, using the rather unappreciated CuI•DMS complex, circumvent problems associated with the formation of dienes. Our preliminary studies show that the dimerization of the alkenyl groups is minimal as long as freshly prepared $(CuI)_4(Me_2S)_3$ complex[7,8] is employed. A vinylzirconocene reagent, in the presence of $(CuI)_4(Me_2S)_3$, is an extremely mild and considerably less basic system than the lithium alkenyl compounds or the corresponding discrete vinylcuprate reagents commonly used in 1,4-addition reactions.

Table 1. Conjugate additions of vinyl groups.

Enone	Alkyne[a]	Cond.[b]	Product	Yield[c]
		12 h		86[d]
		12 h		79[d]
		5 h		54[d] 87[e]
		5 h		78[d]
		2 h		90[d]
		2 h		88[d]
		10 h		84[d]
		10 h		71[d]

[a] 1.0 Equiv alkyne *vs*. enone. [b] 40 °C. [c] Based on isolated and purified material (%). [d] 10 mol% CuI•0.75DMS *vs*. alkyne [e] 100 mol% CuI•0.75DMS, *trans-cis* ratio, 20:1.

1. San Diego State University, Department of Chemistry and Biochemistry, San Diego, CA 92182-1030.
2. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth., Coll. Vol. IX* **1998**, 162–165. See also: Buchwald, S.

L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895–3898.

3. Sun, C. R.; Okabe, M.; Coffen, D. L.; Schwartz, J. *Org. Synth., Coll. Vol. IX* **1998**, 640–643.
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5. El-Batta, A.; Hage, T. R.; Plotkin, S.; Bergdahl, M. *Org. Lett.* **2004**, *6*, 107–110.
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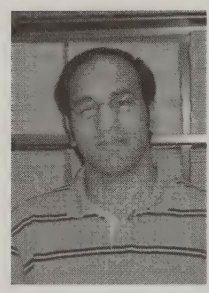
7. Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631–12644.
8. Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182–187.

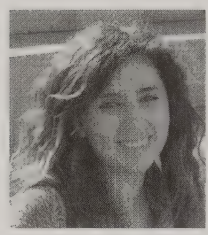
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Schwartz's reagent: Zirconium, chlorobis(η^5-2,4-cyclopentadien-1-yl)hydro- (9); (37342-97-5)
Sodium benzophenone ketyl: Benzophenone, radical ion (1-), sodium (8); Methane, diphenyl-, radical ion (1-), sodium (9); (3463-17-0)
1-Hexyne (8, 9); (693-02-7)
Benzalacetone: 3-buten-2-one, 4-phenyl- (8, 9); (122-57-6)
Copper(I) iodide (8, 9); (7681-65-4)
Dimethyl sulfide: Methyl sulfide (8); Methane, thiobis- (9); (75-18-3)

Mikael Bergdahl received his undergraduate and Ph.D. education at Chalmers University of Technology, Sweden, where he conducted research in the area of organocopper chemistry under the direction of Professor Martin Nilsson†. After postdoctoral work at Notre Dame (Prof. Helquist) and The Scripps Research Institute and University of California, San Diego (Prof. K.C. Nicolaou), he is now conducting research in the area of new chemical methodology and the application toward the synthesis of complex natural products. His current research focuses on the invention and design of catalytic processes, total synthesis and "greener chemistry."



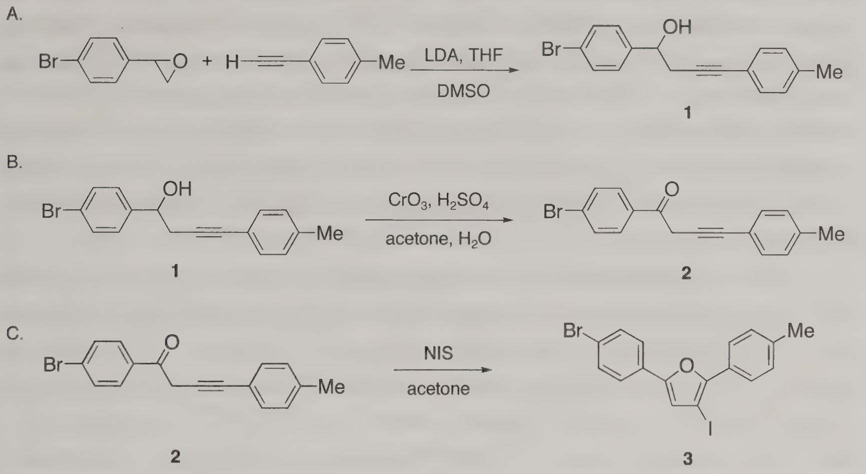
Amer El-Batta received his B.Sc. degree in pharmacy from Applied Science University in Jordan. He then moved to the United States to pursue his graduate studies, where he is currently a Ph.D. candidate in the Joint Doctoral Program of University of California, San Diego and San Diego State University. Under the direction of Prof. Mikael Bergdahl, his graduate research has focused on the copper(I)-catalyzed conjugate addition of alkenylzirconocene and alkenylzincate reagents to various α,β-unsaturated carbonyl substrates. Amer has also been working on chemical studies toward the total synthesis of Azaspirene, a novel angiogenesis inhibitor.



Mónica Trincado was born in 1976 in León, Spain. After undergraduate studies at the Universidad de Oviedo, she joined the group of Prof. José Barluenga in 1999. She obtained her Ph.D. in 2005 on selective iodonium-promoted carbo- and heterocyclization processes. Since November 2005, she has been a postdoctoral scholar (MEC fellow) in the group of Prof. Jonathan Ellman at the University of California, Berkeley on new organocatalytic enantioselective reactions.

Yazmín Rosa-Bauzá was born in 1982 in San Juan, Puerto Rico. She obtained a B.S. in chemistry in 2003 from the Universidad de Puerto Rico, where she conducted research for the group of Prof. José A. Lasalde. She then entered the graduate program of the University of California, Berkeley where she currently pursues her Ph.D. degree in chemistry under the guidance of Prof. Jonathan A. Ellman. Her research focuses on the development of new methods to study the activity of therapeutically important proteases.

ELECTROPHILIC CYCLIZATION WITH *N*-IODOSUCCINIMIDE: PREPARATION OF 5-(4-BROMOPHENYL)-3-IODO-2-(4-METHYLPHENYL)FURAN



Submitted by Adam Sniady, Marco S. Morreale, and Roman Dembinski.[1]
Checked by Cody Timmons and Peter Wipf.[2]

1. Procedure

A. *1-(4-Bromophenyl)-4-methylphenyl)but-3-yn-1-ol* (**1**). A 500-mL, three-necked, round-bottomed flask (Note 1), equipped with a magnetic stirring bar and fitted with a nitrogen inlet adapter and two rubber septa, is charged with THF (40 mL) (Note 2) and 4-ethynyltoluene (4.08 mL, 32.2 mmol) (Note 3) via syringes. The reaction vessel is placed in a dry ice-acetone bath. After 10 min, lithium diisopropylamide solution (LDA) (16.1 mL, 32.2 mmol) (Note 4) is added within 5 min via syringe to the stirred reaction mixture. The mixture is allowed to stir for 10 min after which time the bath is removed and the reaction vessel is allowed to warm to room temperature. Dimethyl sulfoxide (DMSO) (75 mL) (Note 5) is added over 5 min via syringe to the reaction vessel, followed by a solution of 4-bromostyrene oxide (4.94 g, 24.8 mmol) (Note 6) in 5 mL of THF over 1 min via syringe. The reaction mixture acquires a dark red wine color and is allowed to stir at room temperature for 2 h (Note 7). Then, the reaction flask is placed in an ice-bath and quenched with saturated aqueous ammonium

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chloride (100 mL). The mixture is transferred to a 500-mL separatory funnel using saturated aqueous ammonium chloride (50 mL) as a rinse. The aqueous phase is extracted with ether (3 × 150 mL). The combined ether extracts are transferred to a 1-L separatory funnel and washed with saturated aqueous sodium chloride (2 × 200 mL). The organic phase is dried with anhydrous sodium sulfate (10 g) and filtered through a fritted-glass funnel of medium porosity. The solvent is removed via rotary evaporation (23 °C, 25 mmHg) followed by high vacuum (23 °C, 0.6 mmHg, 3 h). The crude product is purified by recrystallization and chromatography of the mother liquor on SiO_2 (Note 8) to yield **1** as a white crystalline solid (6.01 g, 19.1 mmol, 77%) (Note 9).

B. *1-(4-Bromophenyl)-4-methylphenyl)but-3-yn-1-one* (**2**). A 500-mL, single-necked, round-bottomed flask equipped with a rubber septum and a magnetic stirring bar is charged with **1** (6.01 g, 19.1 mmol) and acetone (200 mL) (Note 10). Jones reagent (8.0 mL, 3.0 M solution, 24 mmol) (Note 11) is added by syringe over 5 min at 0 °C (ice-water bath) to the stirred mixture (Notes 12, 13). The bath is removed and the reaction mixture is allowed to stir for an additional 15 min (Note 7), then immediately ether (130 mL) and isopropanol (4 mL) are added. The blue-green solid is filtered off through a medium porosity glass funnel and the filtrate is transferred to a 1-L separatory funnel filled with 100 mL of ice water. Three extractions with ether (3 × 100 mL) are carried out. The combined organic phases are washed twice with saturated sodium bicarbonate (2 × 150 mL), dried over sodium sulfate (10 g), filtered, and concentrated at reduced pressure on a rotary evaporator (23 °C, 25 mmHg). The resulting light yellow solid is transferred to a 50-mL, single neck round-bottomed flask and dried for 6 h under vacuum (23 °C, 0.6 mmHg) to give **2** (5.56 g, 17.8 mmol, 93%), which is used in the next step without further purification (Note 14).

C. *5-(4-Bromophenyl)-3-iodo-2-(4-methylphenyl)furan* (**3**). A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum is charged with **2** (5.10 g, 16.3 mmol). An additional rubber septum with a nitrogen inlet is attached to the remaining neck, and acetone (150 mL) (Note 10) is added via syringe. In a separate flask *N*-iodosuccinimide (NIS) (3.85 g, 17.1 mmol) (Note 15) is dissolved in acetone (60 mL). The solution of NIS is then injected via syringe over 5 min into the reaction mixture that is stirred at room temperature under a nitrogen atmosphere for 2 h. TLC analysis (Note 7) indicates a complete conversion. The solvent is removed by rotary evaporation (23 °C, 25 mmHg) and the residue is extracted with ether (150 mL) (Note 16). The solid (succinimide) is filtered off through a medium porosity glass funnel, and additionally washed with ether (60 mL) (Note 16). The ethereal extracts are combined and transferred to a 500-mL separatory funnel containing 50 mL of a 2.0 M aqueous sodium bisulfite solution. The phases are separated and the aqueous phase is further extracted with ether (3 × 50 mL). The combined organic extracts are washed with brine (1 × 100 mL) and dried over Na_2SO_4 (10 g). The mixture is filtered through a medium porosity fritted glass funnel and the solvent is removed by rotary evaporation (23 °C, 25 mmHg). The resulting material is charged on a column (3 × 40 cm) of silica gel (35 g) (Note 17) and eluted with hexanes/ethyl acetate (8:1) (approximately 600 mL) (Note 18). The product is concentrated by rotary evaporation (23 °C, 25 mmHg) and then dried at 0.6 mmHg (23 °C, 6 h) to yield **3** as a colorless solid (5.80 g, 13.2 mmol, 81%) (Note 19).

2. Notes

1. The apparatus was oven-dried at 135 °C for 2 h and maintained under an atmosphere of dry nitrogen during the course of the reaction. The flasks had neck sizes of 24/40.

2. THF was dried over sodium/benzophenone and freshly distilled under an atmosphere of dry nitrogen.

3. 4-Ethynyltoluene (98%) was purchased from GFS Chemicals and used as received. The checkers used chemicals from Alfa Aesar without further purification.

4. Lithium diisopropylamide (2.0 M solution in THF/*n*-heptane) was purchased from Acros Organics and used as received.

5. Methylsulfoxide, anhydrous, DriSolv was purchased from EMD Chemicals, Inc. and used as received. The checkers used 99.7% anhydrous DMSO from Acros Organics.

6. 4-Bromostyrene oxide (96%) was purchased from Aldrich Chemical Company, Inc. and used as received.

7. The progress of the reaction was monitored by TLC analysis on silica gel eluted with hexanes/ethyl acetate (8:2) and visualized with phosphomolybdic acid. The R_f values were: 0.53 (blue) for 4-bromostyrene oxide, 0.32 (dark blue) for alcohol **1**, 0.59 (blue) for ketone **2**, and 0.74 (orange-brown) for furan **3**.

8. Ethyl acetate (15 mL) was added to the flask containing crude **1** (10.23 g). The flask was heated gently with a heat-gun under hand-stirring until the all of the crude material was dissolved. Then, the solution was layered with hexanes (30 mL) and placed in the refrigerator (–6 °C) for 12 h to induce crystallization. The flask was placed in an ice-bath and the mother liquor was removed via syringe. The crystalline residue was rinsed with cold hexanes (2 × 10 mL) (placed in an ice bath for at least 45 min prior to use) and the rinses were removed via syringe; then the crystalline material was dried (23 °C, 0.6 mmHg, 3 h) to afford alcohol **1** (4.45 g, 14.1 mmol, 57%). The rinses were combined with the mother liquor and the solvent was removed via rotary evaporation (23 °C, 25 mmHg) followed by high vacuum (23 °C, 0.6 mmHg, 3 h) to yield 4.12 g of crude material. This material was dissolved in ethyl acetate (10 mL) with hand-stirring and the help of a heat-gun. The flask was layered with hexanes (20 mL) and placed in the refrigerator for 48 h. Then the crystallization flask was placed into an ice bath and the mother liquor was removed via syringe. The crystalline material was rinsed with cold hexanes (10 mL) and the rinse was removed via syringe; then the crystalline material was dried (23 °C, 0.6 mmHg, 3 h) to afford an additional 6% of alcohol **1** (0.46 g, 1.5 mmol). The rinses and mother liquor were combined and concentrated by rotary evaporation. The resulting material was charged on a column (3 × 40 cm) of silica gel (35 g) and eluted with hexanes/ethyl acetate (6:1) (approximately 400 mL) to provide an additional 14% of alcohol **1** (1.10 g, 3.49 mmol). The total amount of alcohol **1** obtained in this reaction was 6.01 g (19.1 mmol, 77%).

9. mp 133–135 °C (EtOAc/hexanes). Calcd for $C_{17}H_{15}BrO$: C, 64.78; H, 4.80. Found: C, 64.59; H, 4.85. IR (cm^{-1}, NaCl disk) 3411 (m), 1509 (m), 1046 (m), 817 (s). UV-Vis (ε, $M^{-1}cm^{-1}$; ether; 3.5×10^{-5} M) 244 (29000), 254 (24000). MS (rel intensity) 185 (88), 130 (100), 115 (74), 77 (96), 63 (34). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 2.61 (d, 1 H, J = 3.0 Hz), 2.80–2.84 (m, 2 H), 4.90 (td, 1 H, J = 6.3, 1.5 Hz), 7.12 (d, 2 H, J = 7.8 Hz), 7.28–7.33 (m, 4 H), 7.47 (d, 2 H, J = 8.4 Hz); ^{13}C NMR δ: 21.4, 30.6, 71.9, 83.6, 84.5, 119.9, 121.6, 127.5, 129.0, 131.4, 131.5, 138.2, 141.6.

10. High Purity Solvent grade purchased from Burdick & Jackson was used as received. The checkers used OmniSolv High Purity Solvent grade acetone from EMD Chemicals. For procedure B reagent grade acetone can be used.

11. Prepared according to ref.11.

12. Precipitation of blue-green chromium (III) salts was observed.

13. Reaction can be carried out in an open flask.

14. The light yellow solid had a purity of approximately 95% as determined by NMR. A portion of the material (0.46 g) was retained for recrystallization as described in Note 8 to afford colorless crystals for analytical data: mp 121–123 °C (EtOAc/hexanes). Calcd for $C_{17}H_{13}BrO$: C, 65.19; H, 4.18. Found: C, 65.33; H, 4.14. IR (cm^{-1}, NaCl disk) 1677 (s), 809 (s). UV-Vis (ε, $M^{-1}cm^{-1}$; ether; 4.5×10^{-5} M) 254 (35000). MS (rel intensity) 312 (M^+, 53), 183 (100), 155 (60), 129 (74%). ^1H NMR ($CDCl_3$) δ: 2.33 (s, 3 H), 4.02 (s, 2 H), 7.09 (d, 2 H, J = 7.8 Hz), 7.31 (d, 2 H, J = 8.1 Hz), 7.61 (d, 2 H, J = 8.4 Hz), 7.91 (d, 2 H, J = 8.4 Hz); ^{13}C NMR δ: 21.3, 31.5, 80.9, 85.7, 119.7, 128.7, 128.9, 130.1, 131.4, 131.9, 134.1, 138.3, 192.1.

15. NIS was obtained from Simafex and used as received. The checkers used NIS from Alfa Aesar.

16. Ether (unstabilized) was purchased from EMD Chemicals, Inc. and used as received. The checkers used diethyl ether that was freshly distilled from sodium/benzophenone. Extraction with ether stabilized with ethanol led to "leaching" of the succinimide.

17. Sorbent Technologies 60 Å, 230-400 mesh.

18. Flash column chromatography was performed in order to remove residues of succinimide. The solid was dissolved in a minimum amount of hexanes/ethyl acetate (8:1) and loaded onto the column. Pressured air was applied and one fraction was collected.

19. mp 98–100 °C (EtOAc/hexanes). Calcd for $C_{17}H_{12}BrIO$: C, 46.50; H, 2.75. Found: C, 46.72; H, 2.74. IR (cm^{-1}, NaCl disk) 1492 (s), 1475 (s), 1400 (w), 946 (s), 816 (s). UV-Vis (ε, $M^{-1}cm^{-1}$; ether, 2.5×10^{-5} M) 237 (23000), 253 (22000), 330 (35000). MS (rel intensity) 438 (M^+, 100), 283 ($M - C_6H_4Br$, 70). ^1H NMR ($CDCl_3$) δ: 2.42 (s, 3 H), 6.83 (s, 1 H), 7.28 (d, 2 H, J = 8.1 Hz), 7.48–7.59 (m, 4 H), 7.94 (d, 2 H, J = 8.1 Hz); ^{13}C NMR δ: 21.4, 62.1, 116.1, 121.7, 125.2, 126.1, 127.2, 128.5, 129.1, 131.9, 138.4, 151.7, 152.6.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

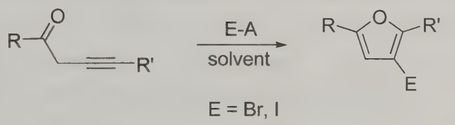
The furan ring is a key component of many pharmaceutical agents, fragrances, natural products, and organic materials. Halofurans allow for further functionalization of the ring, usually via transition metal-catalyzed coupling reactions; they serve as starting materials for combinatorial chemistry.[3] The title molecule includes differently halogenated furan and phenyl rings that can be further functionalized.

The method described herein applies electrophilic cyclization for the synthesis of unsymmetrical 3(*beta*)-iodofurans, with different, but electronically similar substituents in the 2- and 5- (*alpha*) positions. The method is of general use; other 3-halo (iodo- and bromo-) furans can also be synthesized in a regioselective manner (Table 1),[4] using other electrophilic reagents (ICl, NBS, and Br_2). This approach provides a facile, non-acidic, non-basic, non-transition metal based protocol, in which an easy to handle reagent[5] facilitates cyclization and serves simultaneously as a halogen donor. The reaction conditions are mild (room temperature in acetone). The yield is high, the reaction time is relatively short (0.5–2 h), and the isolation procedure is simple.

The best current alternatives for the synthesis of 2,5-unsymmetrically substituted 3-iodofurans include: a) Hydriodic acid cyclization of 4-hydroxybut-2-yn-1-ones.[3,6] This procedure features a strong acid. b) Iodocyclization (3 equiv of iodine) of alk-3-yn-1,2-diols that requires the use of a base.[7] c) Sonogashira coupling-addition-cyclocondensation one-pot procedure that starts from acyl chlorides and terahydropyranyl ethers of propargyl alcohols.[8]

Alkynol **1** was prepared by a known method.[9] It was observed by ^1H NMR that the ring opening of the 2-(4-bromophenyl)oxirane proceeded in a completely regioselective manner. $BF_3 \cdot Et_2O$ was not used as an additive, as reported.[10] THF and DMF were found to be inefficient solvents for this protocol. Alkynone **2** was prepared by oxidation of the alkynol **1** with CrO_3 (Jones reagent).[11] Among other oxidation methods screened, Dess-Martin periodinane[12] was comparable. Jones oxidation for relevant compounds has been reported with low,[13] reasonable,[14,15] and high yields.[16] No experimental procedure, however, was provided for the high yielding example. A catalytic oxidation protocol has also been described.[17] Alk-3-yn-1-ones are reportedly prone to isomerization to the corresponding allenes,[17,18] but this is not pertinent for the procedure for **2**, presumably due to the triple bond stabilization by the conjugated phenyl ring. Alkynone **2** was found to be stable as a solid (stored in a freezer); cycloisomerization was observed when **2** was left for a prolonged time in solution. Cycloisomerization of homologous alk-3-yn-1-ones to the non-halogenated furans has been reported to proceed efficiently with the use of metal catalysts such as Hg,[16] Au,[19] Pd,[15,20] or Zn[21] derivatives.

Table 1. Preparation of other halofurans via electrophilic cyclization.[4]



Entry	*R*	*R'*	*E-A, solvent*	*Yield (%)*
1	C_6H_5	*p*-$CH_3C_6H_4$	NBS, acetone	89
2			NIS, acetone	84
3			ICl, CH_2Cl_2	82
4	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	NBS, acetone	89
5			NIS, acetone	86
6	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	NBS, acetone	83
7			NIS, acetone	94
8	*p*-BrC_6H_4	*p*-*t*-BuC_6H_4	NBS, acetone	87
9			NIS, acetone	81
10	*p*-ClC_6H_4	*p*-*t*-BuC_6H_4	NBS, acetone	86
11			NIS, acetone	88

1. Department of Chemistry, Oakland University, Rochester, MI 48309-4477, USA; dembinsk@oakland.edu
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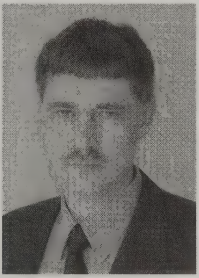
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

5-(4-Bromophenyl)-3-iodo-2-(4-methylphenyl)furan; (852211-52-0)
2-(4-Bromophenyl)oxirane: (4-Bromostyrene oxide); (32017-76-8)
4–Ethynyltoluene; (9766-97-2)
Lithium diisopropylamide; (4111-54-0)
1-(4-Bromophenyl)-4-methylphenyl)but-3-yn-1-ol; (852211-40-6)
Chromium trioxide; (1333-82-0)
1-(4-Bromophenyl)-4-methylphenyl)but-3-yn-1-one; (852211-45-1)
N-Iodosuccinimide (NIS); (516-12-1)



Roman Dembinski was educated at the Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Łódź, Poland (Ph.D. with A. Skowrońska). Before, he completed his undergraduate studies at the Technical University of Łódź. He then joined the research group of J. A. Gladysz at the University of Utah as a research associate. Since 1999 he has held a faculty appointment at the Oakland University, Rochester. His scientific interests include synthetic organic, fluorous, medicinal, and organometallic chemistry.

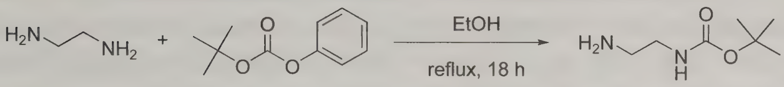
Adam Sniady obtained his M.S. in chemistry from the Technical University of Łódź, Poland, in 2004. Earlier, he received M.S. in Biology from the University of Łódź. He is currently pursuing a Ph.D. with Roman Dembinski at the Oakland University, Rochester, Michigan, USA. His research is focused on developing new synthetic methodologies, including electrophilic cyclizations and synthesis of modified nucleosides.

Marco Morreale obtained his B.A. in chemistry from Wayne State University (Detroit, Michigan) in 1999. During his undergraduate years, his introduction to chemical research began in the laboratory of Norman Lebel. He entered the graduate program in chemistry at Oakland University (Rochester, Michigan) in the fall of 2004. Under the direction of Roman Dembinski, he is currently investigating cyclization strategies for the synthesis of substituted furans.

Cody Timmons received his B.S. (2000) and M.S. (2002) degrees in Chemistry from West Texas A&M University in Canyon, Texas. His M.S. research was performed under the direction of Professor Darren Williams and dealt with the kinetics of the degradation of explosives. He then moved to Texas Tech University in the fall of 2002 and joined the group of Professor Guigen Li, where he studied novel olefin addition and carbon-carbon bond formation methodologies. He completed his Ph.D. in 2006 and is currently a postdoctoral research associate in the lab of Professor Peter Wipf at the University of Pittsburgh, where he is pursuing the total synthesis of ergot and clavine alkaloids.

MONO CARBAMATE PROTECTION OF ALIPHATIC DIAMINES USING ALKYL PHENYL CARBONATES

[(2-Aminoethyl)carbamic acid *tert*-butyl ester]



Submitted by Michael Pittelkow, Rasmus Lewinsky and Jørn B. Christensen.[1]
Checked by Cara Cesario and Marvin J. Miller.

1. Procedure

(2-Aminoethyl)carbamic acid tert-butyl ester. tert-Butyl phenyl carbonate (Note 1) (64.62 g, 61.6 mL, 0.33 mol) is added to a solution of 1,2-ethanediamine (Note 2) (20.0 g, 22.3 mL, 0.33 mol) in absolute EtOH (Note 3)(200 mL) in a 500-mL, single-necked, round-bottomed flask equipped with a stirring bar and a reflux condenser. The reaction mixture is heated gently to reflux overnight (18 h) (Note 4) ensuring that the temperature of the oil bath is at a maximum of 80 °C resulting in a yellow solution. The reaction mixture is cooled to room temperature and the solution concentrated to approximately 150 mL using a rotary evaporator (20 °C, 20 mmHg), which leaves a yellow solution. Water (300 mL) is added and the pH is adjusted to approximately 3 (Note 5) by careful addition of aqueous HCl (2M, approximately 110 mL) followed by extraction with CH_2Cl_2 (3 × 400 mL) (Note 6). The aqueous phase is adjusted to pH 12 by addition of aqueous NaOH (2M, 150 mL) and extracted with CH_2Cl_2 (5 × 500 mL). The combined organic extracts are dried (Na_2SO_4), filtered and concentrated using a rotary evaporator (20 °C, 20 mmHg) to afford 27.0 g (51%) of the title compound as a yellow oil (Notes 7, 8, 9, and 10).

2. Notes

1. *tert*-Butyl phenyl carbonate (98%) was purchased from Aldrich Chemical Company, Inc. and used as received. *tert*-Butyl phenyl carbonate

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is a low melting solid that should be stored in a refrigerator. It is convenient to allow it to melt before handling.

2. 1,2-Ethanediamine was purchased from Aldrich Chemical Company, Inc. (99%). Distillation before use is recommended if the compound has a deep yellow color. Otherwise it can be used as received.

3. Absolute Ethanol (99.9%) was purchased from De Danske Spritfabrikker and was used without further efforts to remove water. The checkers used 200 proof ethanol from Aaper Alcohol and Chemical Company; the solvent was used as received.

4. The Boc protection group is known to be thermally unstable and temperatures above 85–90 °C for prolonged periods should be avoided.[2]

5. The acid labile protective group should not be exposed to acidic aqueous media for prolonged periods of time, otherwise unwanted cleavage of the group may occur.

6. Thorough extraction was needed at this stage to remove unreacted alkyl phenyl carbonate and side products including the bis-carbonate-protected diamine and phenol. Also, it was important to conduct this extraction immediately after addition of 2M HCl, as the Boc group is known to be acid sensitive.

7. The product had the following physical data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (br s, 2 H, NH_2), 1.37 (s, 9 H, $(CH_3)_3$), 2.78 (t, 2 H, $J = 6.0$ Hz), 3.09 (q, 2 H, $J = 6.0$ Hz), 5.18 (br s, 1 H, NHCO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.2, 41.7, 42.2, 78.9, 156.1. MS (FAB): *m/z* 161 (MH^+). IR (film) 3350, 2977, 1693, 1524, 1391, 1366, 1252, 1172. Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.48; H, 10.07; N, 17.48. Found: C, 52.54; H, 9.83; N, 17.28.

8. The level of phenol in the product was below the level that could be detected by the human nose. No other products were detected by NMR and TLC (visualized either by UV light at 256 nm or 316 nm, by oxidation with I_2 or by ninhydrin test).

9. If long-term storage of the product is required, it should be stored under an inert atmosphere as it is prone to react with CO_2 from the air to produce a solid compound.

10. The checkers also performed the procedure on half-scale and obtained 14.4 g (54%) of the title compound as a yellow oil. The submitters report yields ranging from 59-65% when the reaction is performed on the scale of the procedure.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A challenge often encountered in the synthesis, or in the synthetic use of polyamines, is selective protection of the amino groups. This synthetic challenge has been dealt with in a number of ways and elegant multi-step synthetic procedures have been developed to strategically incorporate protection groups in polyamines.[2-4]

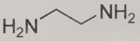
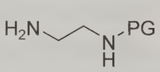
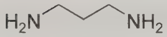
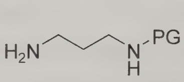
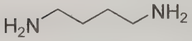
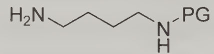
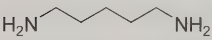
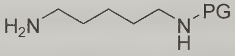
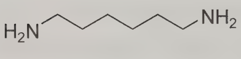
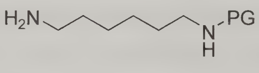
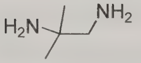
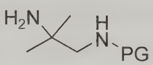
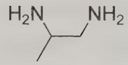
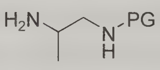
The most widely used procedure for mono carbamate protection of aliphatic diamines is that of Krapcho and co-workers that uses an excess of diamine as compared to di-*tert*-butyl dicarbonate to achieve high yield with respect to the di-*tert*-butyl dicarbonate.[5,6] This procedure, however, is not attractive if the diamine is a valuable intermediate; in general, the use of a large excess of a reagent should be avoided if possible. Other reagents such as 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON)[7] and *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates[8] have also been successful for similar transformations, but issues with strict temperature control and pH control complicates these procedures. The use of alkyl chloroformates has also been described, but these generally give statistical mixtures of products.

This procedure, which uses alkyl phenyl carbonates as the electrophiles, is a simple, efficient and selective method for the preparation of mono-carbamate-protected diamines. It is applicable for large laboratory scale preparations and the purification of the product proceeds without the need for column chromatography, distillation or recrystallization. The procedure has been shown to work almost equally well for the introduction of Boc, Cbz and Alloc protecting groups.[9]

The selectivity in the introduction of carbamate protecting groups has further been tested by reaction with unsymmetrical aliphatic diamines.[9] Selectivity towards reaction with primary amines located on a primary carbon in the presence of a primary amine located on either a secondary or a tertiary carbon was studied by reaction of the alkyl phenyl carbonates with the two diamines, 2-methyl-1,2-propanediamine and 1,2-propanediamine. Both of these diamines were successfully mono-carbamate-protected on the primary amino groups located on the primary carbon atom in high yields with the three carbonates tested (Table 1).

Some representative examples of mono-carbamate-protected diamines prepared by this method are compiled in Table 1, which illustrates the possibility to incorporate the Boc, Cbz and Alloc protecting groups by the same procedure.

Table 1 Selective Carbamate Protection of Aliphatic Diamines.[9]

Amine	Protected Amine	Yield[a]	
		PG = Boc PG = Cbz PG = Alloc	65% 64% 67%
		PG = Boc PG = Cbz PG = Alloc	68% 72% 86%
		PG = Boc PG = Cbz PG = Alloc	63% 63% 77%
		PG = Boc PG = Cbz PG = Alloc	50% 56% 51%
		PG = Boc PG = Cbz PG = Alloc	49% 48% 46%
		PG = Boc PG = Cbz PG = Alloc	91% 97% 96%
		PG = Boc PG = Cbz PG = Alloc	70%[b] 69%[b] 75%[b]

a) PG =Protection Group: Boc = $(CH_3)_3COCO$, Cbz = $PhCH_2OCO$, Alloc = CH_2CHCH_2OCO
b) Yields are based on the polyamine; two equivalents of alkyl phenyl carbonate were used.

1. Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100, Copenhagen Ø, Denmark. E-mail: jbc@kiku.dk
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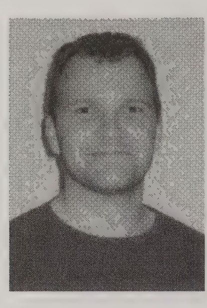
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

tert-Butyl phenyl carbonate: Carbonic acid, 1,1-dimethylethyl phenyl ester; (6627-89-0)

1,2-Ethanediamine; (107-15-3)

Jørn B. Christensen was born in 1960 in Rødovre, Denmark. He received his PhD under the supervision of Professor Klaus Bechgaard in 1994, and became an assistant professor at University of Copenhagen in 1994. He has been associate professor at University of Copenhagen since 1997. He worked part-time in industry at Niels Clauson-Kaas A/S from 1985–1987 and was a visiting scientist at the Technical University of Eindhoven in 1997 and 2001.

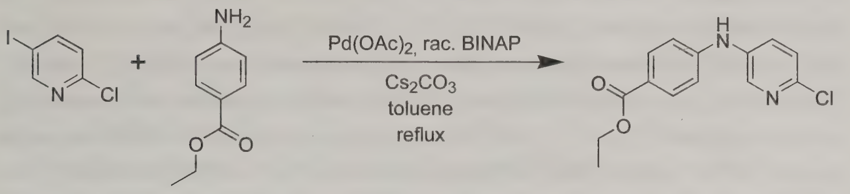
Michael Pittelkow was born in 1977 in Brøndby Strand, Denmark. He received his undergraduate education at the University of Copenhagen and he performed his doctoral work in the laboratories of Associate Professor Jørn B. Christensen. During his studies he has worked in the research groups of Dr. Kevin Winzenberg at CSIRO in Melbourne (Australia), Professor E. W. Meijer the Technical University in Eindhoven (The Netherlands) and Professor J.K.M. Sanders at Cambridge University (United Kingdom). Since November 2006, he has been a FNU postdoctoral scholar working with dynamic combinatorial chemistry at the University of Copenhagen and Cambridge University.



Rasmus Lewinsky was born in 1976 in Gentofte, Denmark. He received his BS at the University of Copenhagen in 2001 after doing his thesis at the University of Adelaide, Australia. He then joined the group of Jørn B. Christensen at the University of Copenhagen where he carried out research in host-guest systems involving dendrimers. Here he received his MS in 2003. He is currently employed at Acadia Pharmaceuticals where he works as a medicinal chemist.

Cara Cesario was born in New York City on November 16, 1979. She received her B.S. degree in 2001 from Stonehill College in North Easton, MA. Cara developed as a synthetic organic chemist at OSI Pharmaceuticals, where she worked on several oncology-driven medical chemistry programs prior to entering the graduate program at The University of Notre Dame. She is currently a graduate student in the laboratory of Marvin J. Miller and is developing novel allylindium methodologies to synthesize highly functionalized carbocyclic scaffolds as novel precursors to biologically important molecules.

SELECTIVE Pd-CATALYZED AMINATIONS ON CHLORO-IODOPYRIDINES: SYNTHESIS OF ETHYL 4-[(6-CHLOROPYRIDIN-3-YL)AMINO]BENZOATE



Submitted by Geert Rombouts,[1] Bert U.W. Maes,[1] Tim H.M. Jonckers,[2] and Kristof T.J. Loones.[1]
Checked by Praew Thansandote[3] and Mark Lautens.[3]

1. Procedure

Ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate. To a 250-mL, one-necked, round-bottomed flask, fitted with a septum pierced with nitrogen inlet and outlet needles, is added $Pd(OAc)_2$ (0.135 g, 0.6 mmol) (Note 1), rac. BINAP (0.374 g, 0.6 mmol) (Note 2) and 100 mL of toluene (Note 3). The mixture is stirred under a nitrogen flow for 15 min. In a 1000 mL round-bottomed, three-necked flask is added 2-chloro-5-iodopyridine (7.183 g, 30 mmol) (Note 4), ethyl 4-aminobenzoate (5.947 g, 36 mmol) (Note 5) and Cs_2CO_3 (48.873 g, 150 mmol) (Note 6). Then, a reflux condenser equipped with a bubbler filled with oil is placed on the three-necked flask and one of the side necks is stoppered. Subsequently, a nitrogen inlet is connected to the remaining neck and the apparatus is flushed with nitrogen for 5 min. Next, under a low flow of nitrogen, the stoppered side neck is opened and the catalyst solution is added through a funnel using 200 mL of toluene (Note 3) to rinse the flask. Under magnetic stirring the resulting mixture is flushed with nitrogen for 10 min. Then, the nitrogen inlet is removed, the neck stoppered and the 1000 mL, three-necked flask placed in a preheated oil bath at 130 °C for 20 h under a nitrogen atmosphere (Note 7). **Vigorous** magnetic stirring is required to prevent precipitation of the base (Note 8). When the reaction mixture is cooled down to room temperature, it is filtered over a sintered glass filter funnel containing Celite® (Note 9) using 1000 mL of EtOAc (Note 10). The filtrate is concentrated at reduced pressure by rotary evaporation at 45 °C (75 mmHg) to afford a brown oil. The residue is

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dissolved in a minimal amount of 99:1 CH_2Cl_2:MeOH (Notes 11 and 12) and loaded on a pre-packed silica gel column (40 x 6 cm, ± 500 g) (Notes 13 and 14). The 99:1 CH_2Cl_2:MeOH eluent is used to isolate ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate, in addition to fractions mixed with ethyl-4-aminobenzoate (Note 15). The impure fractions are collected and concentrated at reduced pressure by rotary evaporation at 45 °C (75 mmHg). The resulting dark beige crystals are then dissolved in a minimum amount of dichloromethane (Note 11) and loaded onto a second pre-packed silica gel column (40 x 6 cm, ± 500 g) (Notes 13 and 14). Pure dichloromethane (Note 11) is used as an eluent until the product begins to elute and subsequently, 99:1 CH_2Cl_2:MeOH is used to afford ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate (7.068 g combined from two purifications, 25.5 mmol, 85%) (Notes 16-20) as a light beige solid.

2. Notes

1. Palladium(II)acetate (47.5 % Pd) was used as received from Acros.
2. (rac)-2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl (98%) was used as received from Acros.
3. Toluene (for analysis, ACS) was used as received from Acros.
4. 2-Chloro-5-iodopyridine (98+%) was used as received from Alfa Aesar. The submitters used this compound as received from Acros.
5. Ethyl 4-aminobenzoate (98%) was used as received from Acros.
6. Cesium carbonate (99.5%) was used as received from Acros for the first trial, and cesium carbonate (99.9%) from Aldrich was used as received for the second trial. No difference in the reactions was observed when using the different sources. Since a large excess (5 equiv) of both bases (Acros and Aldrich) were used and the reaction was only checked after 20 hours at reflux, no differences in conversion between both bases were expected.
7. The checkers used an argon atmosphere with no change in the results of the procedure.
8. In a 500-mL round-bottomed, three-necked flask, a magnetic stirring rate of 700 rpm was used; for the 1000-mL round-bottomed, three-necked flask, the stirring rate was 1000 rpm.

9. A sintered glass filter funnel with a volume of 350 mL, a diameter of 9 cm and a pore size of 0.010–0.016 mm was used. The funnel was filled with Celite® to a height of 6 cm.

10. Ethyl acetate (min. 99%) was used as received from VWR Scientific.

11. Dichloromethane (99.9%) was used as received from VWR Scientific. The submitters used dichloromethane (technical) from Caldic, which was distilled before use.

12. MeOH (99+%) was used as received from Acros.

13. Silica gel (0.040–0.063 mm, pore diameter ca 6 nm) from Silicycle was used. The submitters used silica gel (0.035-0.070 mm, pore diameter approximately 6 nm) from Acros.

14. The pre-packed silica gel column was made by using a slurry of silica gel and the eluent.

15. At this stage, 62% of pure ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate was isolated. Chromatography was performed at ambient pressure to ensure good separation.

16. Before calculating the yield, the reaction product was dried under vacuum (0.5 mmHg) for 20 h.

17. The R_f value of ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate in 94:6 CH_2Cl_2:MeOH was 0.67. The submitters reported an R_f value of 0.16 using TLC plates Alugram® Sil G/UV_{254} from Marcherey-Nagel). Hence, the submitters used this solvent system as a starting eluent for column chromatography, and finished with 92:8 CH_2Cl_2:MeOH once the product began to elute. See Notes 11 and 12 for solvent quality and Note 13 for silica type.

The R_f of ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate in 99:1 CH_2Cl_2:MeOH was 0.31. Thin layer chromatography (TLC) by the checkers was conducted using plates cut from 20 x 20 cm TLC aluminum sheets (Silica gel 60 F_{254} from Merck). See Notes 11 and 12 for solvent quality and Note 13 for silica type.

18. Ethyl 4-[(6-chloropyridin-3-yl)amino]benzoate: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, J = 7.4 Hz, 3 H, CH_3), 4.35 (q, J = 7.6 Hz, 2 H, CH_2), 6.12 (br s, 1 H, NH), 6.99 (d, J = 8.8 Hz, 2 H, H-2',6'), 7.27 (d, J = 8.0 Hz, 1 H, H-3), 7.50 (dd, J = 8.4 Hz, 2.4 Hz, 1 H, H-4), 7.96 (d, J = 8.4 Hz, 2 H, H-3',5'), 8.24 (d, J = 3.2 Hz, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ: 14.4; 60.7, 115.3, 123.1, 124.5, 129.3, 131.6, 137.0, 141.2, 144.2, 146.3, 166.2; HRMS (ESI) for $C_{14}H_{14}ClN_2O_2$ [$M+H^+$] found: 277.0738, calcd: 277.0744; Calcd for

$C_{14}H_{13}ClN_2O_2$: C, 60.85; H, 4.75; Cl: 12.67; N, 10.14; O, 11.59. Found: C, 60.72; H, 4.81; N, 10.0.

19. Elemental analyses were recorded for the checkers on a 2400 Series II CHNS Analyzer. Elemental analysis was recorded for the submitters in the "Hungarian Academy of Sciences" on a Vario EL III (CNHS) (project: GVOP-3.2.1-2004-04-0311/3.0).

20. The procedure as reported enabled the recovery of starting material (ethyl 4-aminobenzoate). Alternatively, the submitters suggested the following procedure to remove residual aniline prior to purification:

Derivatization of the excess aniline to the corresponding acetamide was required in some cases to simplify the purification of the desired reaction product from the excess of aniline. The need for derivatization depended on the chloro-iodopyridine substrate and the specific aniline used. For the synthesis of ethyl 4-[(2-chloropyridin-3-yl)amino]benzoate, derivatization of the excess aniline was used to separate the reaction product from ethyl 4-aminobenzoate. Acetamide formation through the reaction of 4-aminobenzoate with acetyl chloride in refluxing CH_2Cl_2 with triethylamine as base was used to effect derivative formation.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described above is a typical example of the Pd-catalyzed C-5 arylamination of 2-chloro-5-iodopyridine.[4] The observed selectivity is due to chemoselective oxidative addition on the substrate. The weak non-nucleophilic base used in this protocol is essential to obtain broad functional group compatibility.[5] For instance, the traditionally-used MO*t*Bu, which is often employed as the base in Buchwald-Hartwig reactions, is incompatible with the presence of an ester group. If weak bases are used in Buchwald-Hartwig reactions, rate-limiting deprotonation of the Pd(II)-amine intermediate formed in the catalytic cycle is most likely and consequently often observed. Interestingly, the use of a large excess of weak base, although mostly insoluble in the standard solvents used (tetrahydrofuran, dioxane and toluene),[5] speeds up the reactions in those cases.[6] In 2004, our laboratory gained experimental evidence that this remarkable "*base effect*" is due to an interphase deprotonation mechanism of the Pd(II)-amine intermediate formed.[6] Vigorous magnetic stirring of the reaction mixture is, in these cases, essential in order to keep the specific surface area of the base maximal. Interestingly, hitherto there are no other straightforward methods known to allow access to *N*-aryl-2-chloropyridin-5-amines. The selective Buchwald-Hartwig protocol on 2-chloro-5-iodopyridine can also be extended to other chloro-iodopyridines such as 2-chloro-3-iodopyridine, as was recently shown by us and scientists from Merck.[4,6,7]

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4. Maes, B.U.W.; Loones, K.T.J.; Jonckers, T.H.M.; Lemière, G.L.F.; Dommisse, R.A.; Haemers, A. *Synlett* **2002**, 1995.
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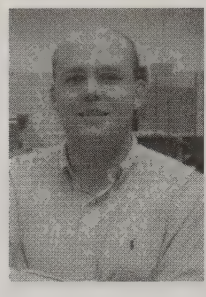
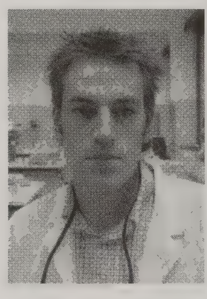
7. Kuethe, J.T.; Wong, A.; Davies, I.W. *J. Org. Chem.* **2004**, *69*, 7752.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Palladium(II) acetate: Acetic acid, palladium(2+) salt: (3375-31-3)
rac. BINAP: Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-; (98327-87-8)
2-Chloro-5-iodopyridine; (69045-79-0)
Ethyl 4-aminobenzoate; (94-09-7)
Cesium Carbonate: Carbonic acid, dicesium salt; (534-17-8)



Bert Maes was born in Sint-Niklaas, Belgium and obtained his Ph.D. in Organic Chemistry in 2001 from the University of Antwerp for his work on new synthetic strategies for the functionalization of the pyridazine nucleus. In October 2001 he was appointed Post-Doctoral Fellow from the Fund for Scientific Research - Flanders (FWO-Vlaanderen). At the University of Antwerp he started his independent research career in the division of Organic Chemistry. In February 2003 he was appointed Professor of Organic Chemistry in the Department of Chemistry of the University of Antwerp. His scientific interests include heterocyclic, organometallic and microwave-assisted chemistry.



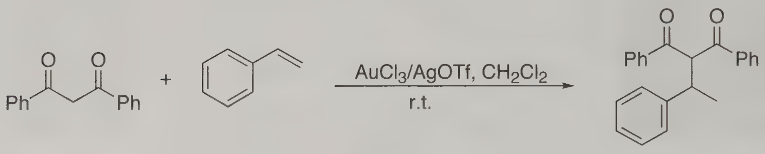
Geert Rombouts was born in 1978 in Borgerhout, Belgium. He followed a Professional Bachelor in Chemistry Education program at the Karel de Grote Hogeschool in Antwerp. For his bachelor thesis he chose the division of Organic Chemistry of the University of Antwerp. After graduation in 2002, he remained in the research group of Professor Maes to work on various academic and industrial projects during which he expanded his skills to a broad range of experimental techniques in different areas of organic chemistry including MAOS, organometallic chemistry and cross-coupling reactions.

Tim Jonckers was born in Antwerp in 1974. He studied Chemistry at the University of Antwerp and obtained his Ph.D. in organic chemistry in 2002. His Ph.D. work covered the synthesis of new necryptolepine derivatives which have potential antimalarial activity. Currently he works as a Senior Scientist at Tibotec, a pharmaceutical research and development company based in Mechelen, Belgium, that focuses on viral diseases mainly AIDS and hepatitis. The company was acquired by Johnson & Johnson in April 2002 and recently gained FDA approval for its HIV-protease inhibitor PREZISTA™.

Kristof Loones was born in Antwerp, Belgium in 1979. In 2001 he obtained his M.Sc. degree in Chemistry from the University of Antwerp. Currently he is a PhD student in the division of Organic Chemistry of the University of Antwerp. His PhD study focuses on the use of the Buchwald-Hartwig reaction in heterocyclic chemistry, in particular he studies tandem metal catalyzed inter- and intramolecular aminations on 2,3-dihaloheterocycles and the accelerating effect of microwave heating.

Praew Thansandote was born in Khon Kaen, Thailand in 1983. She received a Bachelor of Science (B.Sc. Hons) degree in Biopharmaceutical Sciences with top honors at the University of Ottawa in 2001. Following undergraduate research with Mark Workentin at the University of Western Ontario and Keith Fagnou at the University of Ottawa, she is currently a Ph.D. candidate with Mark Lautens at the University of Toronto developing new palladium-catalysed multicomponent reactions. Her awards include a University of Ottawa Medal for the Faculty of Science, a Pfizer Undergraduate Research Fellowship, and NSERC Canada Graduate Scholarships at the Master and Doctoral levels.

HIGHLY EFFICIENT ADDITION OF ACTIVATED METHYLENE COMPOUNDS TO ALKENES CATALYZED BY GOLD AND SILVER



1

Submitted by Chao-Jun Li[1] and Xiaoquan Yao.
Checked by Brian P. Jones and John A. Ragan.

1. Procedure

1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione. An oven-dried, 300-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, a stopcock and a Teflon-coated magnetic stir bar is cooled to room temperature under a flow of nitrogen. While temporarily removing the septum, the flask is charged with gold(III) chloride ($AuCl_3$) (0.303 g, 1 mmol, 5 mol% Au) and silver trifluoromethanesulfonate (AgOTf) (0.77 g, 3 mmol, 15 mol%) (Note 1) under N_2. Dichloromethane (150 mL) (Note 2) is added, and the catalyst mixture is stirred at room temperature for 1.5–2 h, resulting in a brown suspension (Note 3). Dibenzoylmethane (4.48 g, 20 mmol) (Note 4) is added to the reaction flask over 2 min while temporarily removing the septum and the color of the reaction mixture turns green. Styrene (3.45 mL, 30 mmol) (Notes 5, 6) is diluted to 25 mL with CH_2Cl_2 and added dropwise to the reaction mixture by syringe pump through the septum over 6–7 h at room temperature (Note 7). The mixture is then stirred for another 30 min (Note 8). A deep-green solution is obtained (Note 9). The solution is filtered through approximately 40 mL of silica gel in a 60-mL glass Büchner filter funnel to remove the catalyst (Note 10). The silica gel is washed with ether (6 x 50 mL), and the filtrate is concentrated by rotary evaporation at room temperature. The residue, a clear, orange-brown oil, is then purified by flash column chromatography (Note 11) to provide the crude product as a pale yellow solid (6.44 g, 98 %) (Note 12). Further purification is achieved by

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recrystallization. The crude product is dissolved in 30 mL of hot EtOAc, and diluted with 90 mL of hexanes to the point of cloudiness. The mixture is allowed to cool slowly to room temperature overnight, and the resulting solids are collected by filtration, rinsing with 10 mL of hexanes. The solids are air-dried, then placed in a vacuum oven for 4 h to provide analytically pure product as a white solid (4.16 g, 12.7 mmol, 63%) (Notes 13, 14).

2. Notes

1. Gold(III) chloride (99.99%+) and silver trifluoromethanesulfonate (99%+) were purchased from the Aldrich Chemical Company and used as received.
2. Dichloromethane was purchased from J. T. Baker (HPLC grade) and used as received. The submitters distilled their dichloromethane from CaH_2.
3. Silver trifluoromethanesulfonate was stirred with gold chloride in dichloromethane, which resulted in an orange (or slightly brown) precipitate (the clear solution was almost colorless). The clear solution had no catalytic activity.
4. Dibenzoylmethane (98%) was purchased from the Aldrich Chemical Company and used as received.
5. Styrene (99%, inhibited with 10–15 ppm 4-*tert*-butylcatechol) was purchased from the Aldrich Chemical Company and used as received.
6. The main side reaction was the dimerization of styrene, resulting in the formation of 1,3-diphenyl-but-1-ene as the by-product. In order to increase the yield of the major product, excess styrene had to be used. When enlarging the scale of the reaction, the dimerization of styrene became more serious. Therefore, in this case, 1.5 to 2 equiv. of styrene was required.
7. A competition exists between the addition of dibenzoylmethane to styrene and the dimerization of styrene, therefore introduction of styrene in one portion or too quickly resulted in a decreased yield.
8. The submitters stirred the reaction for an additional 4 h. The checkers found that a post-addition stir time ranging from 30 min to 16 h had no impact on product yield or quality.
9. The product was detected by TLC (hexanes/EtOAc = 10/1). R_f (dimer of styrene): 0.91; R_f (diketone): 0.49; R_f (product): 0.29.
10. Length: 3.5 cm diameter × 4 cm. If the catalyst was not removed before evaporation, the product tended to decompose to the diketone and the

dimer of styrene. In a control experiment, when the catalyst was not removed before evaporation (bath temperature of the rotary evaporator: 50 °C), a lower yield was obtained (4.14 g, 63% yield before recrystallization).

11. The oil was diluted with 50 mL of CH_2Cl_2, and 13 g of SiO_2 (Baker, 40 μm, flash chromatography grade) was added. The resulting slurry was concentrated on the rotary evaporator to a tan powder, which was charged to the top of a column prepared from flash silica gel slurried in 2% EtOAc-hexanes (column dimensions 3.5 cm diameter x 18 cm height). Elution with 2% EtOAc-hexanes (1.5 L, removed unreacted dibenzoylmethane) followed by 10% EtOAc-hexanes (6 L) afforded the product in fractions 19-74 (75 mL fractions were collected). The product-containing fractions were combined and concentrated to provide the crude product.

12. The product at this stage was probably suitable for most subsequent applications (ca. 90% purity), but two impurities were observed by ^{1}H NMR and LC/MS and the product failed elemental analysis. LC/MS showed the impurities to be present at ca. 5% each. The impurities appeared to be the two regioisomers (each a mixture of two diastereomers) generated from the addition of dibenzoylmethane to the styrene dimer ($(PhCO)_2CHCH(Ph)CH_2CH(Ph)Me$ and $(PhCO)_2CHCH(CH_2Ph)CH$-$(Ph)Me$): $C_{31}H_{28}O_2$ requires *m/z* 432, M+Na = 455 observed.

13. The submitters recrystallized a sample from 10:1 hexanes-CH_2Cl_2 for elemental analysis and melting point.

14. IR (thin film): ν_{max} 3062, 3028, 2968, 1693, 1662, 1595, 1579, 1494, 1447, 1321, 1264, 1215, 1194, 1180, 979, 907, 756, 732, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (d, *J* = 7.0 Hz, 3 H), 4.07 (dq, *J* = 10.0, 7.0 Hz, 1 H), 5.60 (d, *J* = 10.0 Hz, 1 H), 7.05–7.57 (m, 11 H), 7.73 (d, *J* = 7.5 Hz, 2 H), 8.03 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.1, 41.1, 64.4, 126.5, 127.6, 128.3, 128.3, 128.6, 128.7, 132.9, 133.4, 136.7, 137.0, 143.6, 194.5, 194.8. mp 123–124 °C (lit. 126–127 °C).[2] Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14; Found: C, 84.10; H, 6.06.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

As one of the most common methodologies for the formation of carbon-carbon bonds, the alkylation of 1,3-dicarbonyl compounds usually requires the use of a stoichiometric amount of base and an organic halide. An alternative reaction via transition metal-catalyzed addition of 1,3-dicarbonyl compounds to alkenes would provide a more atom-economical approach and has attracted much interest in recent years.

Recently, Widenhoefer and co-workers reported an elegant intramolecular hydroalkylation of alkenes by carbonyl compounds catalyzed by palladium.[3] Compared with intramolecular addition, intermolecular hydroalkylations of alkenes involving such activated methylene C-H bonds were rarely reported. Widenhoefer reported a platinum- or palladium-catalyzed intermolecular addition of ethylene with *β*-diketones.[4] Hartwig also reported a palladium-catalyzed addition of mono- and dicarbonyl compounds to conjugated dienes.[5]

Using the addition of 2,4-pentanedione to styrene as a prototype, we found:[6] (1) AgOTf or $AuCl_3$ provided only trace amounts of the desired product, (2) the combination of $AuCl_3$ and AgOTf provided the desired product in good yields, (3) changing the counter ion of the silver salt from OTf lowered the yield, but no difference was observed when the counter ion of gold was changed, and (4) CH_2Cl_2 was the solvent of choice relative to DCE and nitromethane. It should be noted that since the catalytic system is very strongly Lewis acidic, THF was not stable in the solution of the gold/silver catalyst. THF decomposed almost immediately, and a semi-solid was obtained in the tube.

A side reaction observed in this system was the polymerization of styrene, in which the dimerization promoted by metal triflate species was found to be the main reaction and gave 1,3-diphenyl-but-1-ene as the main by-product.[7] Since styrene readily dimerized in the reaction, the use of catalytic $AuCl_3$/AgOTf in CH_2Cl_2 with an excess of styrene, which was diluted and slowly added to the reaction, provided the best yield. It should be mentioned that dimerization became more serious with an increase in the reaction scale, especially for the less reactive 1,3-diketone substrates, such as 2,4-pentandione. In these cases, increasing the excess of styrene and reaction temperature was beneficial. Alternatively, use of a more diluted solution and slower addition helped to inhibit the dimerization of styrene. The results of various 1,3-diketones and styrenes are summarized in Table 1.

Since gold(III) chloride is expensive, decreasing the amount of catalyst was also attempted. For the less active diketones, such as 2,4-pentandione, reduction of the amount of gold(III) resulted in a decrease in yield. However, for the procedure described above, there was only ca. 3% decrease in yield.

This reaction was reversible at higher temperatures when catalyzed by gold or silver catalyst.[8] Dibenzoylmethane derivatives were most prone to the reverse reaction, which gave the diketone and the styrene dimer. In small scale reactions (1 mmol or less), the reversibility was not a serious problem, since it was not necessary to remove CH_2Cl_2 before separation. However, for larger scale reactions, the catalyst had to be removed by a short silica gel column before concentration, especially for the dibenzoylmethane derivatives (although it was not necessary for the 2,4-pentanedione derivatives).

Under the same reaction conditions, various cyclic dienes and cyclic enol ethers were reacted with dibenzoylmethane and 1-benzoylacetone (Table 2).[9] Addition to a triene (entry 2) was also selective in the generation of a diene product. The reaction had to be carried out at low temperature in some cases in order to prevent polymerization or dimerization of the diene (entries 3 and 4). The use of cyclic alkenes bearing a heteroatom (entries 5-8) resulted in selective product formation. However, addition of dibenzoylmethane to an ether-substituted DHP (entries 6 and 7) led to a significant amount of bis-alkylation products. The use of simple cyclic and acyclic alkenes led to very low conversions, while use of acyclic conjugated dienes resulted in the formation of a complicated unidentified mixture. The use of sterically hindered dienes or less activated methylenes (such as 2,4-pentadione and cyclic diketones) also led to low conversions under the present conditions.

Table 1 Addition of β-Diketone to Alkenes Catalyzed by Gold Catalyst[a]

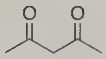
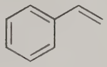
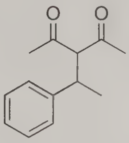
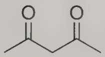
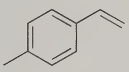
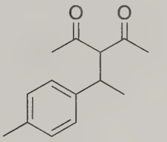
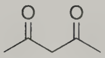
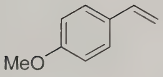
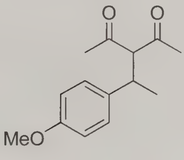
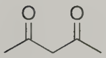
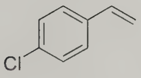
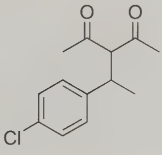
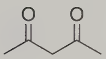
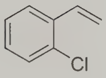
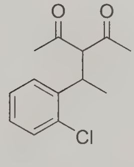
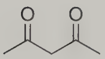
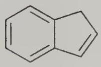
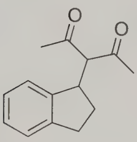
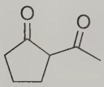
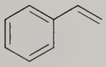
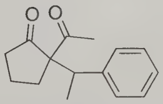
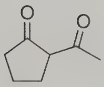
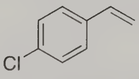
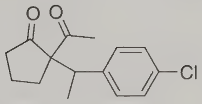
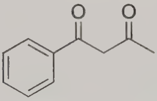
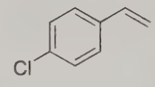
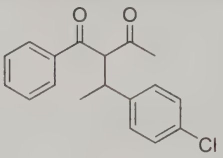
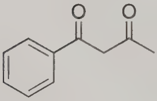
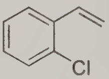
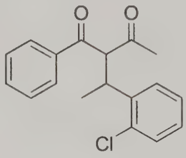
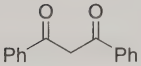
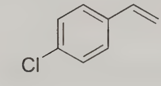
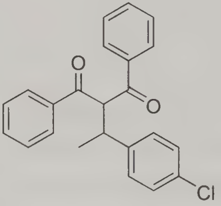
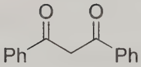
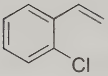
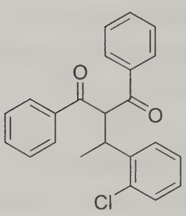
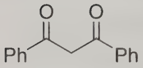
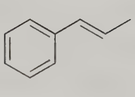
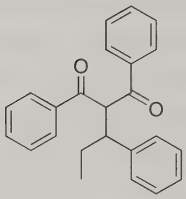
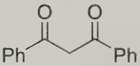
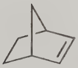
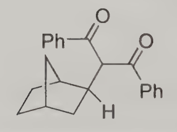
Entry	β–Diketone	Alkenes[b]	Product	Yield (%)[c]
1				89[d]
2				94
3				62
4				97
5[e]				50
6				44
7				70 (1:1)[f]
8				55 (1:1)[f]

Table 1 (continued)

Entry	β-Diketone	Alkenes[b]	Product	Yield (%)[c]
9				89[d] (1:1)[f]
10				67 (1:1)[f]
11				98
12				91
13				39[g]
14				81

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[a] Reaction conditions: 1 mmol scale in dichloromethane. [b] The alkenes (1.5 equiv., diluted to 3 mL) were added by syringe pump over 5 h. [c] Isolated yield. [d] This reaction was also carried out on a 30 mmol scale (2 equiv. of styrene was used), and 70–74% yields were achieved. [e] The reaction was carried out in refluxing nitromethane. [f] The ratio of two diastereomers was determined by ^{1}H-NMR. [g] Approximately 56% of the diketone was recovered.

Table 2 Addition of β-diketone to cyclic alkenes catalyzed by gold catalyst[a]

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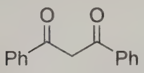
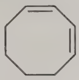
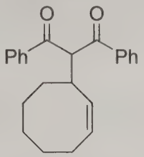
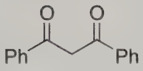
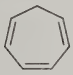
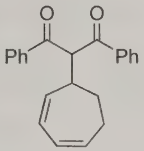
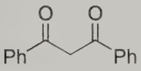
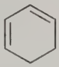
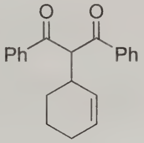
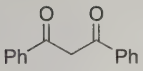
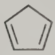
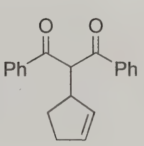
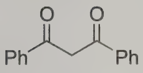
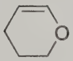
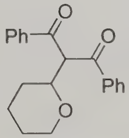
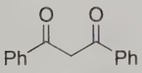
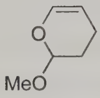
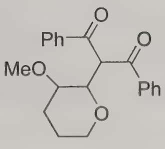
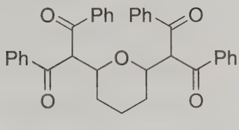
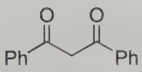
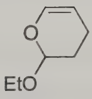
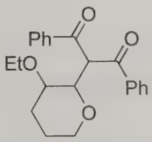
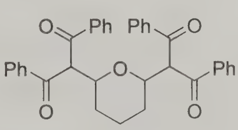
1				65
2[d]				42
3[e]				51
4[e]				50
5[e]				68
6			 47 +  15	
7			 44 +  15	

Table 2 (continued)

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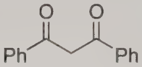
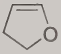
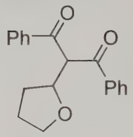
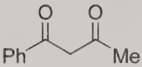
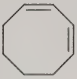
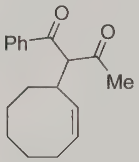
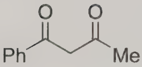
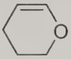
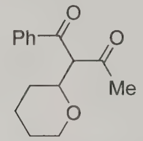
8				58
9				38 (1.4:1)[f]
10				35 (1.2:1)[f]

[a] Reactions were performed in dry dichloromethane. [b] Alkenes were added by syringe pump. [c] Isolated yield. [d] The position of the double bonds was confirmed by COSY-NMR. [e] Reactions were run at 0 °C. [f] The ratio of the two diastereoisomers was determined by ^{1}H NMR.

1. Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec H3A 2K6, Canada
2. Gonzalez, A.; Marquet, J.; Moreno-Manas, M. *Tetrahedron Lett.* **1988**, *29*, 1469.
3. (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290; (b) Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 650; (c) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056. (d) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (e) Wang, X.; Pei, T.; Han, X.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 2699. See also (f) Yang, D.; Li, J. H.; Gao, Q.; Yan, Y. L. *Org. Lett.* **2003**, *5*, 2869.
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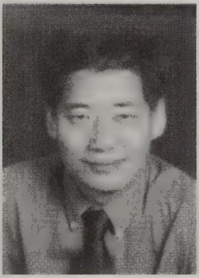
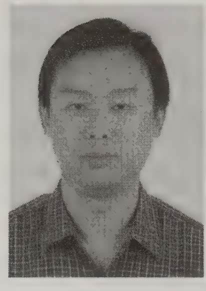
8. Yao X.; Li, C.-J. *J. Org. Chem.* **2005**, *70*, 5752.
9. Nguyen, R.-V.; Yao, X.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dibenzoylmethane: 1,3-Propanedione, 1,3-diphenyl-: (120-46-7)
Styrene: Benzene, ethenyl-: (100-42-5)
Gold(III) chloride; (13453-07-1)
Silver trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, silver(1+) salt; (2923-28-6)
1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione: 1,3-Propanedione, 1,3-diphenyl-2-(1-phenylethyl)-; (116140-58-0)



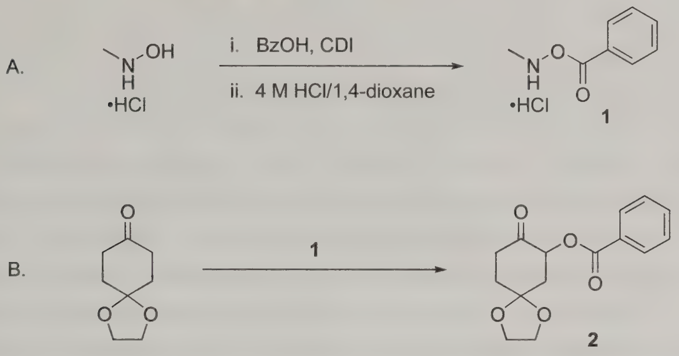
Chao-Jun Li (born in 1963) received his BS at Zhengzhou University, MS at the Chinese Academy of Sciences in Beijing and Ph.D at McGill University in 1992, with T. H. Chan and D. N. Harpp. He spent 1992-94 as a NSERC Postdoctoral Fellow with B. M. Trost at Stanford University. He was an Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000-2003) at Tulane University, and a visiting faculty (with Robert G. Bergman) at University of California at Berkeley (2002). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts focus on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and possess high “atom-efficiency”.



Xiaoquan Yao was born in 1973 in Nanjing, China. He received his B.Sc. at Nanjing Normal University in 1995, and his Ph.D. at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences in 2000 with Prof. Huilin Chen. He spent 2001-2002 as a postdoctoral fellow in Prof. Xiyan Lu's laboratory at Shanghai Institution of Organic Chemistry, CAS and then another postdoctoral stint at McGill University in Canada with Prof. Chao-Jun Li (2003-2006). He is currently working as a faculty member at Nanjing University of Aeronautics & Astronautics in China. His current research interests are focused on metal-mediated C-C bond formation reactions in water and organic materials.

Brian Jones was born in 1975 in Warwick, Rhode Island. He received his B.S. and M.S. degrees from Worcester Polytechnic Institute in 1997 and 1998 respectively. While in school, he worked as a Co-op student in the Medicinal Chemistry department at Pfizer in Groton, CT. Upon graduation he joined the Pfizer Chemical Research and Development group where he currently works as a process chemist.

A PRACTICAL PROCEDURE FOR CARBONYL α-OXIDATION: SYNTHESIS OF (2-BENZOYLOXY)-1,4-CYCLOHEXANEDIONE *MONO*-ETHYLENE KETAL



Submitted by Teyrnon C. Jones and Nicholas C. O. Tomkinson.[1]
Checked by Kalyani Patil and Peter Wipf.[2]

1. Procedure

A. *N-Methyl-O-benzoylhydroxylamine hydrochloride* **1** (Note 1). Benzoic acid (18.32 g, 150.0 mmol, 1 eq.) (Note 2) is placed in an open single-necked 500-mL round-bottomed flask equipped with a large magnetic stirrer and dissolved in 200 mL of methylene chloride (Note 3). This clear solution is cooled to 0 °C in an ice-water bath before the controlled addition of carbonyldiimidazole (24.32 g, 150.0 mmol, 1 equiv.) over a period of five min (Note 4). The ice bath is removed and the resultant yellow solution is stirred at ambient temperature until all effervescence has ceased (15 minutes). After this period, *N*-methylhydroxylamine hydrochloride (15.87 g, 190.0 mmol, 1.27 equiv.) is added in one portion to the reaction mixture and stirring is continued for a further 40 min at 25 °C. The reaction broth is diluted with 100 mL of methylene chloride, transferred to a 1-L separatory funnel and washed sequentially with cold (0 °C) 1 M hydrochloric acid (300 mL) (Note 5) and saturated sodium hydrogen carbonate solution (300 mL). The organic layer is separated, dried using sodium sulfate (40 g), filtered through a Büchner funnel and concentrated to dryness in a 500-mL round-bottomed flask on a rotary evaporator (25 °C, 20 mmHg). Diethyl ether (200 mL) is added to the resulting liquid followed by 4 M HCl in dioxane (75 mL, 0.30 mol, 2 equiv.) (Note 6). After 30 minutes, the solid precipitate is collected in a Büchner funnel (Note 7), washed with 100 mL of ice-cold diethyl ether and dried under high vacuum (0.5 mmHg) for 8 h to give *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **1** as a white microcrystalline solid (17.45 g, 62%) (Note 8) that is used in Step B without further purification (Note 9).

B. *(2-Benzoyloxy)-1,4-cyclohexanedione (mono)ethylene ketal* **2**. An open 25-mL single-necked round-bottomed flask (Note 10) equipped with a magnetic stirring bar is charged at ambient temperature with 1,4-cyclohexanedione mono-ethylene ketal (4.68 g, 30.0 mmol, 1 equiv.) (Note 11) and dimethyl sulfoxide (7.5 mL). *N*-Methyl-*O*-benzoylhydroxylamine hydrochloride **1** (5.63 g, 30.0 mmol, 1 equiv., as prepared above) is added to the flask over a period of 15 min (Note 12) and the reaction mixture is stirred for 1 h (Note 13). The solution is subsequently poured into 300 mL of ethyl acetate and transferred to a 1-L separatory funnel where it is washed with 250 mL of water. The layers are separated and retained: the organic layer is washed further with two 250 mL portions of water, which are discarded; and the original aqueous layer is washed with two 100 mL portions of ethyl acetate which are added to the original organic layer. The combined organic fractions are dried using magnesium sulfate (25 g), filtered through a Büchner funnel and concentrated on a rotary evaporator (40 °C, 20 mmHg) to give a brown solid as a crude product (Note 14). The crude solid is transferred to a 25-mL Erlenmeyer flask and dissolved in 5 mL of hot (80 °C) isopropyl alcohol, then allowed to slowly cool to room temperature. The resultant solid is collected in a Büchner funnel and sequentially washed with ice-cold isopropyl alcohol (50 mL) and ice-cold 35-60 petroleum ether (50 mL) (Note 11) before being dried under high vacuum (0.5 mmHg) for 8 h to yield (2-benzoyloxy)-1,4-cyclohexanedione mono-ethylene ketal **2** (Note 15) as pale yellow needles (6.38 g, 77%) (Note 16).

2. Notes

1. Procedure A is a modification of the method of Geffken: Geffken, D. *Chem. Ber.* **1986**, *119*, 744.

2. Benzoic acid (99+%), carbonyldiimidazole, *N*-methylhydroxylamine hydrochloride (98%), and 4 M hydrochloric acid in 1,4-dioxane were obtained from Aldrich Chemical Company, Inc.

Methylene chloride and diethyl ether were obtained from Fisher Scientific Ltd. Submitters purchased benzoic acid (98%) from Avocado Research Chemicals Ltd. and carbonyldiimidazole (97%) from Lancaster Synthesis Ltd. All chemicals were used as received.

3. There was no need to oven-dry the vessels used in the reaction, and all steps were carried out in flasks open to the atmosphere.

4. The reaction produced carbon dioxide gas, resulting in vigorous effervescence.

5. The hydrochloric acid was prepared by dilution of 12 M hydrochloric acid purchased from EMD Chemicals Inc.

6. The submitters generated hydrochloride acid gas from a slow addition of sulfuric acid to ammonium chloride and bubbled the gas directly into the diethyl ether solution.

7. Filtration should be carried out in a fume hood as the mother liquor contains dissolved hydrogen chloride.

8. The checkers performed the reaction also at 50%, 25%, and 10% scale. The yields ranged from 58-62%.

9. Physical properties and spectral data for **1** are as follows: mp 135–137 °C; IR (nujol) 2923, 1770, 1599, 1475, 1260 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6) δ: 2.90 (s, 3 H), 7.57 (t, $J = 7.8$ Hz, 2 H), 7.72 (t, $J = 7.5$ Hz, 1 H), 7.95 (d, $J = 7.2$ Hz, 2 H), 11.38 (brs, 2 H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 36.7, 126.4, 129.6, 129.8, 135.1, 163.7; MS (EI) *m/z* (rel intensity) 151 ($[M-HCl]^+$, 11), 136 (25), 123 (24), 122 (87), 107 (8), 106 (70), 105 (56); HRMS (EI) calculated for $C_8H_9NO_2$ 151.0633, found 151.0631; Anal. calcd. for $C_8H_{10}NO_2Cl$ C, 51.2, H, 5.4, N, 7.5, Cl, 18.9; found C, 51.3, H, 5.5, N, 7.5, Cl, 18.9.

10. There was no need to oven-dry the reaction flask, and the reaction was carried out open to the atmosphere.

11. 1,4-Cyclohexanedione mono-ethylene ketal (97%) was obtained from Aldrich Chemical Company, Inc. Dimethyl sulfoxide (99.9%) was obtained from Fisher Scientific Ltd. Isopropyl alcohol and 35-60 petroleum ether was obtained from J. T. Baker Chemical Co. Submitters used dimethyl sulfoxide (99%) purchased from Aldrich Chemical Company, Inc., and, isopropyl alcohol and 40-60 petroleum ether purchased from Fisher Scientific Ltd. All chemicals were used as received.

12. It was noted that this reaction was exothermic. Measuring of the internal reaction temperature with a thermometer showed that during the addition of **1** the temperature rose to a maximum of 70 °C.

13. The progress of the reaction was monitored by TLC analysis on EMD Silicagel 60 F_{254} 0.25 mm silica plates, using 50% ethyl acetate/35-60 petroleum ether as eluent and visualising with potassium permanganate solution. The ketone starting material had an $R_f = 0.37$ and the oxidized product had an $R_f = 0.51$.

14. Occasionally, the crude product was obtained as a brown oil. In these cases the oil may solidify on standing or can be induced to crystallize by the addition of a small amount of 35-60 petroleum ether, which was subsequently removed by rotary evaporation.

15. The checkers performed the reaction also at 50%, 25%, and 10% scale. The yields ranged from 78-81%.

16. Physical properties and spectral data for **2** are as follows: mp 114-116 °C; IR (dichloromethane) 2964, 1720, 1451, 1274, 1111, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.01–2.12 (m, 2 H), 2.27 (t, J = 12.8 Hz, 1 H), 2.45–2.51 (m, 2 H), 2.80 (dt, J = 14.2, 6.6 Hz, 1 H), 4.04–4.13 (m, 4 H), 5.68 (q, J = 6.6 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 8.08 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.5, 35.8, 40.3, 64.9, 65.0, 73.6, 107.3, 128.4, 129.5, 129.8, 133.2, 165.3, 203.3; MS (EI) *m/z* (rel intensity) 276 (M^+, 16), 219 (25), 171 (22), 155 (23), 126 (16), 122 (20), 115 (12), 105 (100); HRMS (EI) calculated for $C_{15}H_{16}O_5$ 276.0997, found 276.1000; Anal. calcd. for $C_{15}H_{16}O_5$ C, 65.2, H, 5.8; found C, 65.1, H, 5.8.

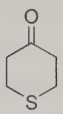
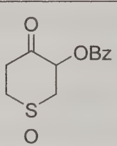
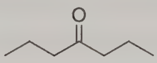
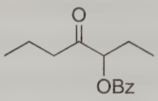
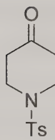
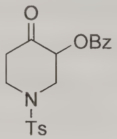
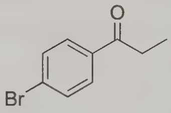
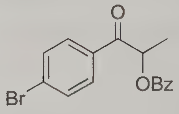
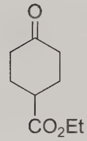
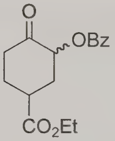
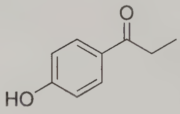
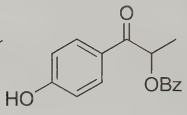
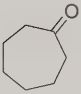
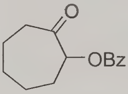
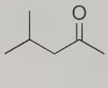
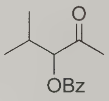
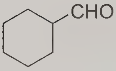
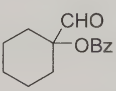
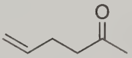
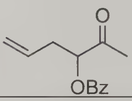
3. Discussion

α-Oxyacylated carbonyl compounds are important functional groups present in many natural products, pharmaceuticals and synthetic intermediates of broad utility. Shi and coworkers have reported the catalytic asymmetric introduction of the oxybenzoyl group α- to ketone carbonyl groups by the low temperature epoxidation of preformed enol esters followed by rearrangement under acidic conditions, which furnishes products in good yields and excellent enantioselectivity.[3] The preparation of α-acetoxy ketones catalyzed by iodobenzene via a hypervalent iodine intermediate has also been described.[4] Despite the effectiveness of this method, it has not been extended to aldehyde substrates and is only effective for the introduction of acetoxy groups. Discrimination between primary and non-sterically encumbered secondary carbon centers is also poor using this method.

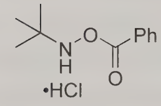
The procedure described above provides a very practical alternative for the α-acyloxylation of carbonyl compounds. The reagents are bench stable and react under mild conditions with both aldehydes and ketones in good yields. Not only do these reagents avoid air-sensitive intermediates and therefore obviate the need for purified solvents and specialized equipment; but the reagents display a remarkable functional group tolerance and useful chemo- and regioselectivity.

N-Methyl-*O*-benzoylhydroxylamine hydrochloride **1** is a general reagent for the oxygenation of both aldehydes and ketones.[5] The related *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochloride **3** allows the chemoselective α-oxybenzoylation of aldehyde substrates in good to excellent yield, since it is completely inert to ketones.[6] Both classes of reagents can be used for the introduction of the oxyacyl group of choice by simple modification of the carboxylic acid used in the reagent synthesis. Representative examples for the α-functionalization of aldehydes and ketones by *N*-alkyl-*O*-acylhydroxylamine hydrochlorides are given in Tables 1 and 2.

TABLE 1
α-Oxybenzoylation of Aldehydes and Ketones using *N*-Methyl-*O*-Benzoylhydroxylamine Hydrochloride (**1**)

Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1			75[a]	6			90[b]
2			74[a]	7			82[c]
3			75[a]	8			85[c]
4			69[a]	9			73[b]
5			74[a]	10			81[b]

[a] DMSO, rt, 4-24 h, 1 equiv. **1**; [b] DMSO, 50 °C, 24 h, 1 equiv. **1**; [c] DMSO, 50 °C, 48 h, 2 equiv. **1**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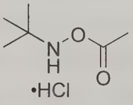
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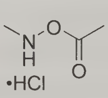
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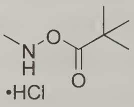
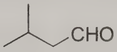
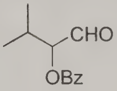
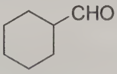
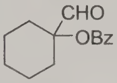
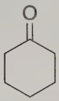
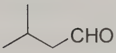
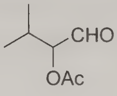
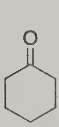
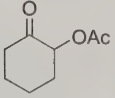
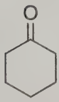
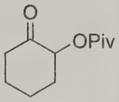

6

TABLE 2
α-Acyloxylaton of Carbonyl Compounds using *N*-Alkyl-*O*-Acyl Hydroxylamine Hydrochlorides (3-6)

Entry	Reagent	Substrate	Product	Yield (%)
1	**3**			79[a]
2	**3**			82[a]
3	**3**		None	0[a]
4	**4**			72[a]
5	**5**			67[b]
6	**6**			69

[a] THF/H_2O (9:1), 50 °C, 24 h; [b] DMSO, rt, 24 h

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2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA; pwipf@pitt.edu.
3. (a) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818; (b) Feng, X.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2831.
4. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244.
5. Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729.
6. Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Benzoic acid; (65-85-0)

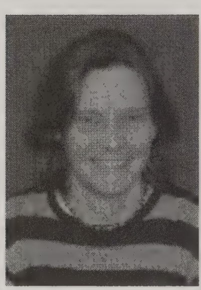
Carbonyldiimidazole: 1*H*-Imidazole, 1,1'-carbonylbis-; (530-62-1)

N-Methylhydroxylamine hydrochloride: Methanamine, *N*-hydroxy-, hydrochloride; (4229-44-1)

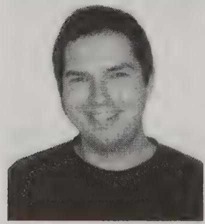
N-Methyl-*O*-benzoylhydroxylamine hydrochloride: Methanamine, *N*-(benzoyloxy)-, hydrochloride; (27130-46-7)

1,4-cyclohexanedione mono-ethylene ketal: 1,4-Dioxaspiro[4.5]decan-8-one; (4746-97-8)

(2-Benzoyloxy)-1,4-cyclohexanedione (mono)ethylene ketal: 1,4-Dioxaspiro[4.5]decan-8-one, 7-(benzoyloxy)-; (872312-37-3)



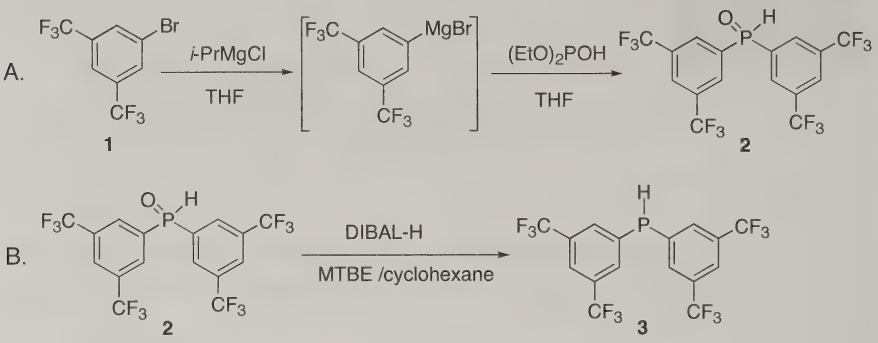
Nick Tomkinson was born in St Andrews, Scotland in 1969. He studied Chemistry at The University of Sheffield and received his BSc in 1992. His Ph.D. studies were under the supervision of Dr. D. Neville Jones and Professor Jim Anderson investigating asymmetric synthesis with unsaturated sulfur compounds. Postdoctoral studies on Nuclear Receptors were undertaken with Dr. Tim Willson at GlaxoSmithKline, Research Triangle Park, North Carolina (1996-1998). Nick was appointed to the staff at Cardiff University in 1999 and in 2004 was awarded an EPSRC Advanced Research Fellowship.



Teyrnon Jones was born in 1978 and raised in Anglesey, North Wales. He received his MChem from The University of Sheffield in 2000, and following completion of his undergraduate studies chose to remain at Sheffield to research new applications of germanium-linked solid-phase organic synthesis in the laboratory of Dr. Alan Spivey. Subsequent to the award of his Ph.D. in 2004, an interest in metal-free synthesis and organocatalysis lead to a successful two-year postdoctoral collaboration with Dr. Nick Tomkinson at Cardiff University developing new practical methods for carbonyl α-oxygenation. He is currently senior scientist in Medicinal Chemistry at AstraZeneca, Loughborough UK, working in the respiratory and inflammation therapeutic area.

Kalyani Patil obtained her B.Sc. (1998) in Chemistry from the University of Mumbai, India. She completed her M.Sc. in 2000 from the Indian Institute of Technology, Bombay under the guidance of Professor Sujata Bhat. Her M.Sc. thesis involved the synthesis of dienones for applications in the synthesis of bioactive molecules. She then moved to North Dakota State University to pursue her Ph.D. under the supervision of Professor Mukund Sibi, where her research was focused on the synthesis of β-amino acids via free radical chemistry. After completion of her Ph.D. in 2005 she joined the group of Professor Peter Wipf at the University of Pittsburgh as a postdoctoral research associate and is currently working on the synthesis of the tetracyclic core of viridin.

SYNTHESIS OF ELECTRON-DEFICIENT SECONDARY PHOSPHINE OXIDES AND SECONDARY PHOSPHINES: BIS[3,5-BIS(TRIFLUOROMETHYL)PHENYL]PHOSPHINE OXIDE and BIS[3,5-BIS(TRIFLUOROMETHYL)PHENYL]PHOSPHINE



Submitted by Carl A. Busacca, Jon C. Lorenz, Paul Sabila,
Nizar Haddad, and Chris H. Senanyake.[1]
Checked by Scott E. Denmark and Christopher S. Regens.

1. Procedure

A. *Bis[3,5-bis(trifluoromethyl)phenyl]-phosphine oxide* (**2**). To an oven-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stir-bar, and fitted with a graduated 250-mL pressure-equalizing addition funnel (fitted with a septum) in the center neck, a thermocouple inserted through a rubber septum in the left neck, and an inert gas inlet valve in the right neck, is evacuated (0.03 mmHg vacuum) and backfilled three times with argon. The flask is charged with 3,5-bis(trifluoromethyl)bromobenzene **1** (59.2 mL, 343 mmol, 3.3 equiv, Note 1) followed by anhydrous THF (60 mL, Note 2) through the addition funnel septum cap with a syringe. The addition funnel is then charged with isopropylmagnesium chloride (171.5 mL, 343 mmol, 3.3 equiv, 2.0 M solution in THF, Note 3) via cannula under argon pressure. The flask is then placed in a dry-ice/acetone bath. When the internal temperature reaches –30 °C, the solution of isopropylmagnesium chloride is added rapidly over 10 min. The internal temperature at the conclusion of the addition is –60 °C. Tetrahydrofuran (10 mL, added through the addition funnel septum cap with

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a syringe) is used to wash the walls of the addition funnel into the flask. The dry-ice/acetone bath is then replaced by an ice/H_2O bath. The internal temperature rapidly rises to a maximum of 9 °C in approximately 5 min, to give a clear, brown solution, then the internal temperature rapidly falls to 2 °C (Note 4). At this time a 50 μL aliquot is removed by syringe through the septum in the left neck of the flask, and is quenched into a biphasic mixture of Et_2O/2 M HCl (~ 2 mL). The aqueous layer is removed and the organic solution is back extracted with H_2O (1 mL). The organic layer is filtered through a SiO_2 plug (1 mm x 2 cm), which is eluted with Et_2O (~2 mL). The filtrate is analyzed by gas chromatography to monitor reaction progress (Notes 5 and 6). An additional portion of isopropylmagnesium chloride solution (5 mL, 10 mmol, 3% of the original Grignard charge) is added at once by syringe at 1 °C through the septum in the left neck of the flask. After an additional 0.5 h, GC analysis of a quenched aliquot indicates that Grignard exchange is complete (total reaction time 1 h after the initial exotherm).

The addition funnel is then charged with THF (30 mL) followed by diethyl phosphite (13.7 mL, 104 mmol, 1 equiv, Note 7) through the septum cap with a syringe. The reaction solution is again cooled in a dry-ice/acetone bath. When the internal temperature reaches –60 °C, the phosphite solution is added drop-wise over 10 min, causing the internal temperature to rise to –50 °C. The cold bath is removed, and the reaction is allowed to warm to ambient temperature (~18-20 °C). After one hour at ambient temperature, GC analysis of a quenched aliquot indicates the reaction is complete to give phosphine oxide **2** (t_R = 6.90 min, GC Method 2). The reaction mixture is then cooled to 5 °C internal temperature in an ice/H_2O bath, and 3 N HCl (175 mL) is added by addition funnel over 15 min. The addition funnel is removed and saturated aqueous NaCl solution (150 mL) is then added at once. Then EtOAc (250 mL) is added and the biphasic mixture is transferred to a 1-L separatory funnel. The phases are separated and the aqueous phase is back-extracted with EtOAc (250 mL). The combined organic extracts are then dried ($MgSO_4$, 50 g, Note 8), filtered into a 1-L round-bottomed flask and the solvent is removed with rotary evaporation under reduced pressure. The residue is further dried under high vacuum (0.02 mmHg, 15 min) to remove the 1,3-bis(trifluoromethyl)benzene by-product (Note 9). The resulting orange-brown solid is dissolved in boiling MTBE (90 – 110 mL) in a 1-L round-bottomed flask, equipped a magnetic stir-bar, and a 125-mL pressure-equalizing addition funnel with an argon adaptor at the top. The contents are allowed to cool to ambient temperature under argon, with stirring, causing a thick, brown slurry to form (Note 10). Hexanes (140 mL) are added over 10 min to this slurry through the addition funnel (Note 11). The mixture is then stirred for an additional 10 min to break up any large solids, and the mixture is filtered through a medium-fritted filter funnel, washing the flask and filter cake with MTBE (5 mL). The solid is dried under a vigorous stream of argon, from an inverted funnel, flowing over the filter cake. After 2 h, compound **2** (36.0–37.1 g, 73–75%) is obtained as a powdery, white solid (Note 12).

B. *Bis[3,5-bis(trifluoromethyl)phenyl]phosphine* (**3**). A 500 mL, three-necked, round-bottomed flask containing a magnetic stir-bar is fitted with a 125-mL pressure-equalizing addition funnel (fitted with a rubber septum) in the center neck, a thermocouple through a rubber septum in the left neck, and an inert gas valve in the right neck. Phosphine oxide **2** (10.0 g, 21.0 mmol, 1 equiv) is added under a flow of argon by removal of the inert gas valve. After replacement of the inert gas valve, MTBE (50 mL, Note 13) is added via syringe to the flask through the septum on the addition funnel. The resulting slurry is stirred under argon at ambient temperature for 5 min. The addition funnel is then charged with DIBAL-H (42.2 mL, 42.2 mmol, 1.0 M solution in cyclohexane, 2 equiv, Note 14). This solution is then added drop-wise to the substrate slurry over 10 min. The internal temperature rises to a maximum temperature of 36 °C and a brown solution forms (Fig. 1). The addition funnel is rinsed with MTBE (5 mL). The resulting mixture is then stirred for 1 h, and then is placed in a dry-ice/acetone bath. A needle connected to an argon source is inserted through the flask septum and positioned beneath the solution surface, so that a slow stream of argon is bubbled through the solution (Note 15). The addition funnel is charged with an aqueous 2 N NaOH solution (80 mL). This solution is added drop-wise to the reaction mixture over ~ 15 min. The internal temperature rises to –27 °C during the addition (Note 16). The cold bath is replaced by a water bath (30–35 °C) to raise the internal temperature to approximately 20 °C, and the mixture is stirred for an additional 15 min at this temperature (Note 17). Stirring is stopped, and two clear phases are observed (See Fig. 2). A 32-cm, 18-gauge needle attached to a 60-mL polyethylene syringe is inserted through the flask septum with the needle tip pressed against the bottom of the flask. The lower (aqueous) phase is removed by syringe and discarded as waste. The addition funnel is charged with H_2O (40 mL) by syringe through the addition funnel septum cap and added to the reaction flask by slow addition over approximately 5 min. The mixture is stirred for 5 min, then the lower (aqueous) phase is removed by syringe through flask septum and discarded as waste, leaving the solution of crude secondary phosphine **3** in the reaction flask.

An Airfree filter is charged with Merck silica gel 60 (32 g) followed by anhydrous $MgSO_4$ (28 g), and topped with sand (30 g) (Note 18, see Fig. 1). The filter is then sealed with a rubber septum that is further secured with a piece of copper wire. The bottom of the Airfree filter is connected to a vacuum take-off adapter (Note 19), which in turn is connected to a 500-mL, one–necked, round-bottomed flask used as receiver. The side arm of the vacuum take-off adapter is connected with a short piece of rubber tubing to a Florence flask cold trap (Note 20) that is cooled to –78 °C in a dry-ice/acetone bath to collect the evaporated organic solvents. The cold trap is vented to an argon bubbler. All joints of the Airfree filter apparatus are greased with Dow silicon grease (Note 21). A mixture of cyclohexane/MTBE (5:1, 100 mL) is then injected by syringe through the septum cap of the Airfree funnel containing the silica gel/$MgSO_4$ column. A slight argon pressure is applied from the upper valve of the Airfree filter, and the solvent is passed through to wet the solids. The receiver flask is removed and the wash solvent discarded as waste. A new, oven-dried, 500-mL one-necked receiver flask is then installed, and argon is purged gently through the system for approximately 5 min. The organic phase from the reaction flask containing the crude secondary phosphine is removed by syringe and injected through the septum cap of the Airfree filter onto the column (see Fig. 3). At the same time, a cyclohexane/MTBE mixture (5:1, 100 mL) is charged to the reaction flask by syringe (Notes 15, 22). A slight positive pressure of argon is applied to the upper valve of the Airfree filter as before, slowly flowing the secondary phosphine solution through the column. Then, 100 mL of the solvent mixture is injected through the septum cap of the Airfree filter and is passed through the solids under a slight argon pressure to wash the remaining column contents into the receiver flask. The entire product is now contained in the 500-mL receiver flask (Fig. 4, Note 23).

The receiver flask is placed in a warm water bath (32 – 40 °C) (Note 24). The rate of argon flow through the Airfree filter side arm is then increased, causing the solvents to be removed from the secondary phosphine product by evaporation, with solvent condensation in the attached cold trap (Note 25). After approximately 8 h, all the solvent is removed and the product secondary phosphine **3** (7.7–7.8 g, 79–83% yield) is obtained as a white crystalline solid in the receiver (Fig. 5, Note 26).

The secondary phosphine can be recrystallized by working in a dry box. The solid is transferred to a one-necked, 100-mL, round-bottomed flask equipped with a magnetic stir-bar, and a septum-sealed, Teflon-taped three-way adaptor. The flask is removed from the dry-box and the adaptor is attached to an argon inert gas line. A 20-gauge needle is inserted through the septum as a vent, then degassed MeOH (18 mL) is added via syringe. The contents are then magnetically stirred and heated with a heat gun until all the solids dissolved. The needle is removed and the flask is isolated from the septum by turning the three-way stopcock. The contents are allowed to cool to ambient temperature. When the contents became turbid (Fig. 6), the flask is placed in an ice bath for 1 h. While still in the ice-bath, the mother-liquor is cannula-transferred to another septum–sealed, one-necked, 100-mL, round-bottomed flask that is purged three times with argon. The crystals remaining are washed with chilled (0 °C) degassed MeOH (5 mL) and the wash is transferred to the flask containing the mother liquor. The crystals are further dried under reduced pressure (0.03 mmHg) for 30 min and then are transferred to the dry-box for isolation (crop 1, 6.0–6.3 g, 61–64%). The flask containing the mother liquor is transferred to the dry-box and placed in a –20 °C freezer for 12 h. A second crop is collected by vacuum filtration in the dry box to give 0.90–0.36 g (combined crops 6.7–6.9 g, 68–70%) of **3** as colorless needles (Note 27).

2. Notes

1. 3,5-Bis(trifluromethyl)bromobenzene (98%) was purchased from Matrix Scientifics and used as received.
2. Anhydrous THF (99.9%, stabilized with ~25 ppm BHT) was purchased EMD and used as received.
3. Formation of this Grignard reagent from Mg metal is hazardous and must not be done. Old solutions of isopropylmagnesium chloride of

uncertain concentration should not be used. Isopropylmagnesium chloride in THF was purchased from Aldrich Chemical Co. in a ®-SurePac cylinder. The solution of isopropylmagnesium chloride *was* titrated as 2.0 M, using both no-D NMR[12] and the procedure of Watson and Eastham.[13]

4. The temperature of the Grignard exchange reaction was critical: If the batch temperature was not allowed to exotherm as described, exchange was incomplete, and products derived from addition of unreacted isopropylmagnesium chloride to the phosphite were ultimately formed. An undercharge of isopropylmagnesium chloride was also less problematic than an overcharge of isopropylmagnesium chloride for the same reason.

5. Analytical gas chromatography (GC) was performed using a Hewlett-Packard 5890 Gas Chromatograph fitted with a flame ionization detector. Two GC methods were used. GC Method 1: Injections were made onto a Hewlett-Packard HP1 (30 m x 0.32 mm) capillary column. Injector temperature was 250 °C; the detector temperature was 300 °C with a H_2 carrier gas flow of 16 mL/min. The column temperature program was as follows: 50 °C for 1 min, 50 °C to 150 °C at 25 °C/min, hold at 150 °C for 5 minutes. Total run time 12 min. GC Method 2: Injector temperature is 250 °C; the detector temperature is 300 °C with a H_2 carrier gas flow of 16 mL/min. The column temperature program is as follows: 50 °C for 1 min, 50 °C to 250 °C at 25 °C/min, hold at 250 °C for 3 minutes. Total run time 12 min. Retention times (t_R) are obtained using Agilent Chemstation software or a Hewlett-Packard 3396 Series II Integrator.

6. At this point, 4% of aryl bromide **1** (retention time, t_R, = 2.88 min, GC Method 1) still remained, and 1,3-bis(trifluoromethyl)benzene was present at t_R = 1.47 min.

7. Diethyl phosphite (98%) was purchased from Aldrich Chemical Co. and used as received.

8. Some phosphine oxides can crystallize as hydrates, so the organic solution had to be well dried to avoid these forms.

9. Rotary evaporation was preformed at 25 mmHg and the water bath temperature was 40 °C. The boiling point of 1,3-bis(trifluoromethyl)benzene is 116 °C. If the aromatic impurity was not removed, it lowered the yield of the crystallization by partially solubilizing phosphine oxide **2**.

10. The large amounts of solids were difficult to dissolve in MTBE initially. Multiple heating cycles (3-4) using an oil bath (65 °C) were used to

completely dissolve all solids. In one case 110 mL of MTBE was needed to complete solubilize the solid.

11. Hexanes was added to maximize the yield of the crystallization. It could be omitted with a ~5% reduction in yield.

12. Data for **2** were as follows: mp 127–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.12 (s, 2 H), 8.21 (d, J = 13.1 Hz, 4 H), 8.33 (d, $^1J_{HP}$ = 507 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 122.5 (C(5), q, $^1J_{CF}$ = 273.0 Hz), 127.2 (C(4), m), 130.8 (C(2), dq, $^2J_{CP}$ = 13.1 Hz, $^3J_{CF}$ = 4.5 Hz), 133.1 (C(1), d, $^1J_{CP}$ = 100.4 Hz), 133.2 (C(3), dq, $^2J_{CF}$ = 34.0 Hz, $^3J_{CP}$ = 13.0 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 15.47 ($^1J_{PH}$ = 505 Hz); ^{19}F NMR (469 MHz, $CDCl_3$) δ: –63.65; IR (Nujol) cm^{-1}: 3080 (w), 3057(w), 3031(w), 2389 (w), 2210 (w), 1619 (m), 1329 (m), 1277 (s), 1196 (s), 1134 (s), 1002 (w), 960 (s), 914 (s), 845 (s), 681 (s); MS (EI, 70 ev) *m/z* (%): 474 (M^+ (100)), 472 (40), 456 (11), 455 (59), 453 (21), 407 (20), 261 (35), 195 (71); Anal. Calcd for $C_{16}H_7F_{12}OP$: C, 40.53; H, 1.49; F, 48.08; Found C, 40.45; H, 1.45; F, 47.82.

13. Anhydrous MTBE (99.8%) was purchased from Aldrich Chemical Co. and was used as received. DIBAL-H/cyclohexane was purchased from Aldrich Chemical Co. and was titrated to 1.0 M using no-D NMR[12] and gas titration according to the method of Brown.[14]

14. DIBAL-H is a pyrophoric material, and standard inert atmosphere syringe and cannula transfer methods were used.

15. All secondary phosphines are air-sensitive compounds. Careful maintenance of inert conditions was critical to successful isolation of these compounds.

16. The initial portion of the quench was very exothermic, and slow addition of the aqueous base was required. Some ice (H_2O) formed, yet was of no consequence. Gas (isobutane and possibly H_2) was formed during the quench, also requiring controlled addition.

17. Full hydrolysis of all carbon-aluminum bonds required ambient temperature conditions. If hydrolysis was incomplete, clogging of the silica gel column by the organic phase occurred.

18. A Chemglass Airfree filter (AF-0542-25) was used. The order of addition of solids to the Airfree filter was critical: The phosphine solution needed to first encounter $MgSO_4$ (top of column) so that the *dried* solution flowed through the silica gel. The solvent system was chosen to allow for elution of non-polar phosphines and retention of more polar impurities.

19. A Chemglass vacuum take-off adapter (Chemglass CG-1049-01) was used.

20. A Florence flask cold trap (Kontes 926400-0500) was used.

21. Dow Silicone grease part no. 2021846-0702.

22. Oxygen, a non-polar gas, has a higher solubility in non-polar solvents such as these than in polar solvents. All organic solvents were degassed for 30 min prior to use by bubbling argon through the solution in a two-necked, 1-L round-bottom flask, equipped with septa in both joints. One septum was pierced and a gas dispersion tube was used to bubble argon through the solution. The other septum contained a 20-gauge needle for a bleed.

23. For many applications of secondary phosphines, this solution was used immediately for the next step (nucleophilic addition, cross-coupling, phosphine-borane formation, etc.), rather than isolating the phosphine in neat form. The solution was collected in a three-neck flask, for example, which served as the reactor for the next step. The solvents used here (MTBE/C_6H_{12}) were chosen to be compatible with these further transformations.

24. The water bath was essential for rapid evaporation of the solvent. The water bath temperature was not allowed to exceed 55 °C, because product sublimation was observed at higher temperatures, which lowered the overall yield of phosphine **3**.

25. The cold trap improved the efficiency of the solvent removal, and avoided venting the solvents to the atmosphere. A combination of this argon sweep with an applied vacuum can be used to remove solvent, though increased product oxidation was observed under these conditions.

26. The yield was determined by weighing the solid in a dry-box. From the evaporation procedure, the secondary phosphine was obtained in 90–95% purity, where phosphine oxide was the major contaminant. The submitters noted that the amount of phosphine oxide did not affect subsequent transformations with the secondary phosphine.

27. Data for **3**: mp 67–70 °C. ^{1}H NMR (500 MHz, C_6D_6) δ: 4.61 (d, $^1J_{HP}$ = 223.3 Hz, 1H), 7.53 (d, J = 6.1 Hz, 4H), 7.65 (s, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ: 123.0 (q, $^1J_{CF}$ = 273.6 Hz), 123.5 (m), 132.6 (dq, J = 5.9, 34.1 Hz), 134.0 (d, J = 18.4 Hz), 137.4 (d, J = 17.5 Hz); ^{31}P NMR (202 MHz, C_6D_6) δ: –41.66 ($^1J_{PH}$ = 223 Hz); ^{19}F NMR (471 MHz, C_6D_6) δ: –63.29; IR (Nujol) cm^{-1}: 2319 (w), 1839 (w), 1820 (w), 1616 (w), 1280 (s),

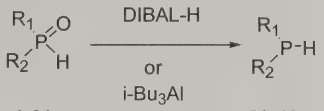
1173 (s), 1125 (s), 1093 (s), 923 (m), 901 (s), 896 (s), 848 (m), 704 (s), 684 (s); MS (EI, 70 ev) *m/z* (%): 458 (M^+ (51)), 439 (28), 244 (46), 195 (100), 175 (68); Anal. Calcd for $C_{16}H_7F_{12}P$: C, 41.94; H, 1.54; F, 49.76; Found C, 41.82; H, 1.49; F, 50.27.

3. Discussion

This procedure can be used to prepare a variety of secondary phosphines by reduction of secondary phosphine oxides (SPO's), as we have recently reported.[2] The SPO's are in turn prepared from the combination of Grignard reagents and diethyl phosphite. The arylmagnesium reagent prepared in situ here must be prepared by Knochel Grignard exchange,[3] not from Mg metal.[4] This method successfully reduces all classes of SPO's from electron-deficient to electron-rich, even extremely hindered species such as di-*tert*-butylphosphine oxide and dimesitylphosphine oxide (Table 1). The conditions are mild and the reducing agents are among the cheapest available. The reductions are chemoselective, and according to adiabatic calorimetry, are also safe, with typical adiabatic temperature rises of only ~17 °C.

Diphenyldisilane has been used for SPO reductions,[5] but reaction temperatures exceed 200 °C and the silane currently costs ~ $90/mol, more than 50 times the cost of DIBAL-H. Lithium aluminum hydride has been used for this reduction,[6] yet material handling and quenching is hazardous, and primary phosphine impurities are generated with electron-deficient SPO's. Phenylsilane has been employed,[7] but a non-aqueous workup with distillation of the product is required. Many secondary phosphines, such as the one described here, are solids that cannot be readily distilled. Furthermore, when using phenylsilane as the reductant, polysiloxanes are known by-products that must be removed. Phosphorus trichloride in combination with lithium aluminum hydride has been used to generate secondary phosphines from SPO's.[8] This method has the disadvantages of taking two steps rather than one (usually requiring the distillation of the intermediate chlorophosphine, which is often difficult) along with the problems associated with lithium aluminum hydride mentioned above. Trichlorosilane has been used for this reduction,[9] but it has a very low boiling point, 31 °C, and is then routinely used at temperatures 80–100 °C *above* its boiling point (refluxing toluene or xylene), creating a hazard. In addition, trichlorosilane works only for electron-rich SPO's that are capable of nucleophilically attacking silicon, and it is commonly used in very large excess (5–20 equivalents). Trichlorosilane is also about twice as expensive

Table 1. Reduction of Secondary Phosphine Oxides by iisobutylaluminum Hydride and Triisobutylaluminum.



1-21 **22-42**

Entry	R_1	SM	R_2	Time/ Temp. (°C)	Al species [a]	Prod	Yield
1	C_6H_5	**1**	C_6H_5	10m/25	**D**	**22**	86
2	4-F-C_6H_4	**2**	4-F-C_6H_4	10m/25	**D**	**23**	90
3	4-Cl-C_6H_4	**3**	4-Cl-C_6H_4	10m/25	**D**	**24**	83
4	4-Me-C_6H_4	**4**	4-Me-C_6H_4	10m/25	**D**	**25**	80[b]
5	3-F-C_6H_4	**5**	3-F-C_6H_4	10m/25	**D**	**26**	89
6	3-Cl-C_6H_4	**6**	3-Cl-C_6H_4	10m/25	**D**	**27**	81
7	3-F, 5-Me-C_6H_3	**7**	3-F, 5-Me-C_6H_3	10m/25	**D**	**28**	82
8	3,5-F_2, 4-OMe-C_6H_2	**8**	3,5-F_2, 4-OMe-C_6H_2	10m/25	**D**	**29**	90
9	3,5-Cl_2-C_6H_3	**9**	3,5-Cl_2-C_6H_3	1h/-20	**D**	**30**	90
10	3,5-F_2-C_6H_3	**10**	3,5-F_2-C_6H_3	1h/-20	**D**	**31**	80
11	2-Me-C_6H_4	**11**	2-Me-C_6H_4	8h/25	**D**	**32**	80
12	4-NMe_2-C_6H_4	**12**	4-NMe_2-C_6H_4	45m/25[c]	**D**	**33**	92
13	4-OMe-C_6H_4	**13**	4-OMe-C_6H_4	40m/25 [c]	**D**	**34**	91
14	2-OMe-C_6H_4	**14**	2-OMe-C_6H_4	8h/35 [c]	**D**	**35**	75
15	C_6H_5	**15**	*i*-Pr	10m/25	**D**	**36**	90
16	C_6H_5	**16**	*t*-Bu	4h/50	**D**	**37**	86
17	n-Bu	**17**	*n*-Bu	1h/25	**D**	**38**	85
18	C_6H_{11}	**18**	C_6H_{11}	4h/50	**D**	**39**	88
19	t-Bu	**19**	*t*-Bu	4h/50	**D**	**40**	87
20	3,5-$(CF_3)_2$-C_6H_3	**20**	3,5-$(CF_3)_2$-C_6H_3	15m/25	**D**	**41**	72
21	3-F, 5-Me-C_6H_3 + PhI [d]	**7**	3-F, 5-Me-C_6H_3 + PhI [d]	30m/25	**T**	**28**	82
22	3-F, 5-Me-C_6H_3 + $PhCONMe_2$ [d]	**7**	3-F, 5-Me-C_6H_3 + $PhCONMe_2$ [d]	30m/25	**T**	**28**	81

23	2,4,6-Me$_3$-C$_6$H$_2$	**21**	2,4,6-Me$_3$-C$_6$H$_2$	24h/70 [e]	**T**	**42**	75

[a] **D** = DIBAL-H; **T** = *i*-Bu$_3$Al. [b] Yield of phosphine borane complex [c] 5 eq. DIBAL-H used [d] competition experiment [e] 8 eq. i-Bu$_3$Al used

as DIBAL-H per mole on a metric ton basis. Finally, borane has been utilized for this reduction.[10] Disadvantages of this reagent include the generation of phosphinous acid borane impurities (a form of unreacted starting material), the need to use a large excess, and a recent severe industrial accident on storage.[11] In summary, the organoaluminum reduction method described here is superior to existing methods in substrate scope, mildness of conditions, chemoselectivity, number of steps, operability, safety, and cost.

Figure 1: DIBAL-H Reduction Prior to Quench

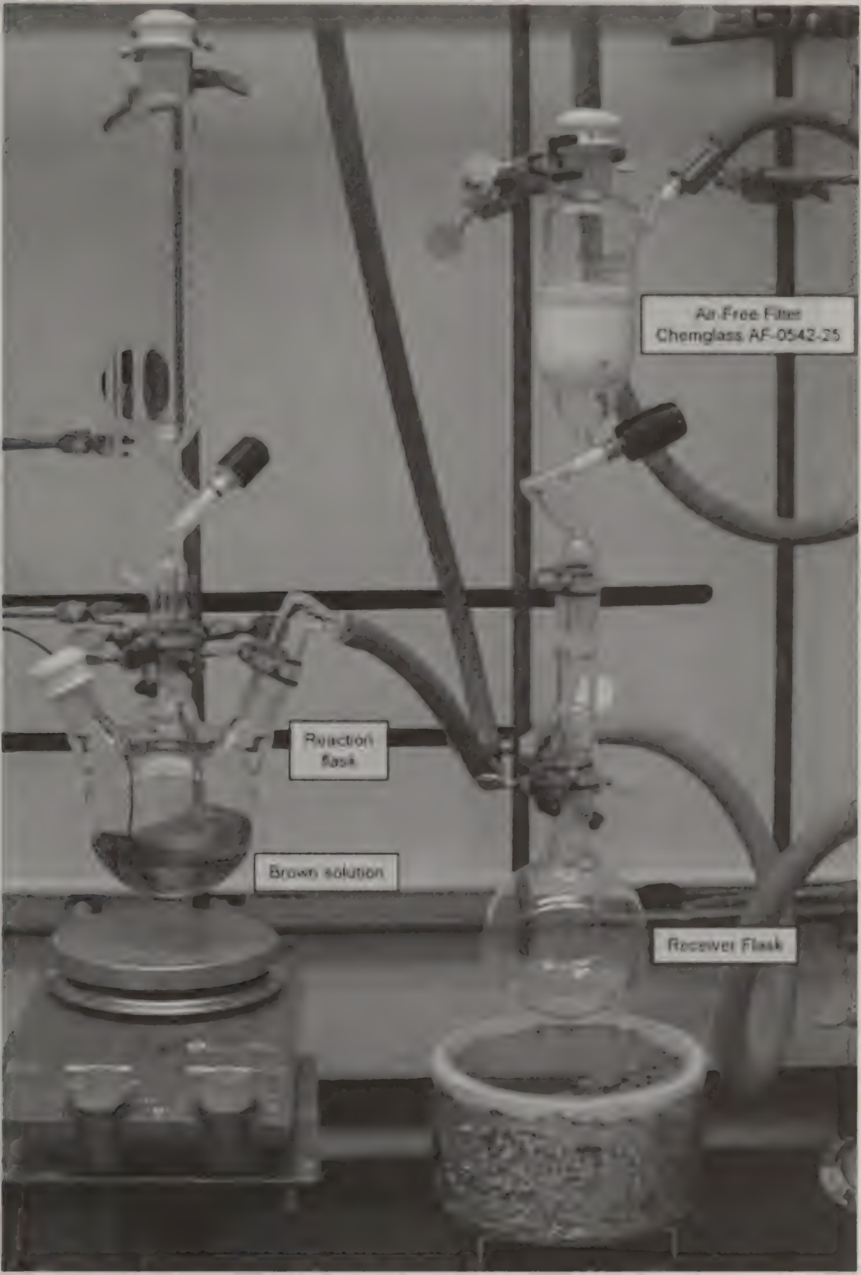


Figure 2: Reaction Mixture After Aqueous Quench

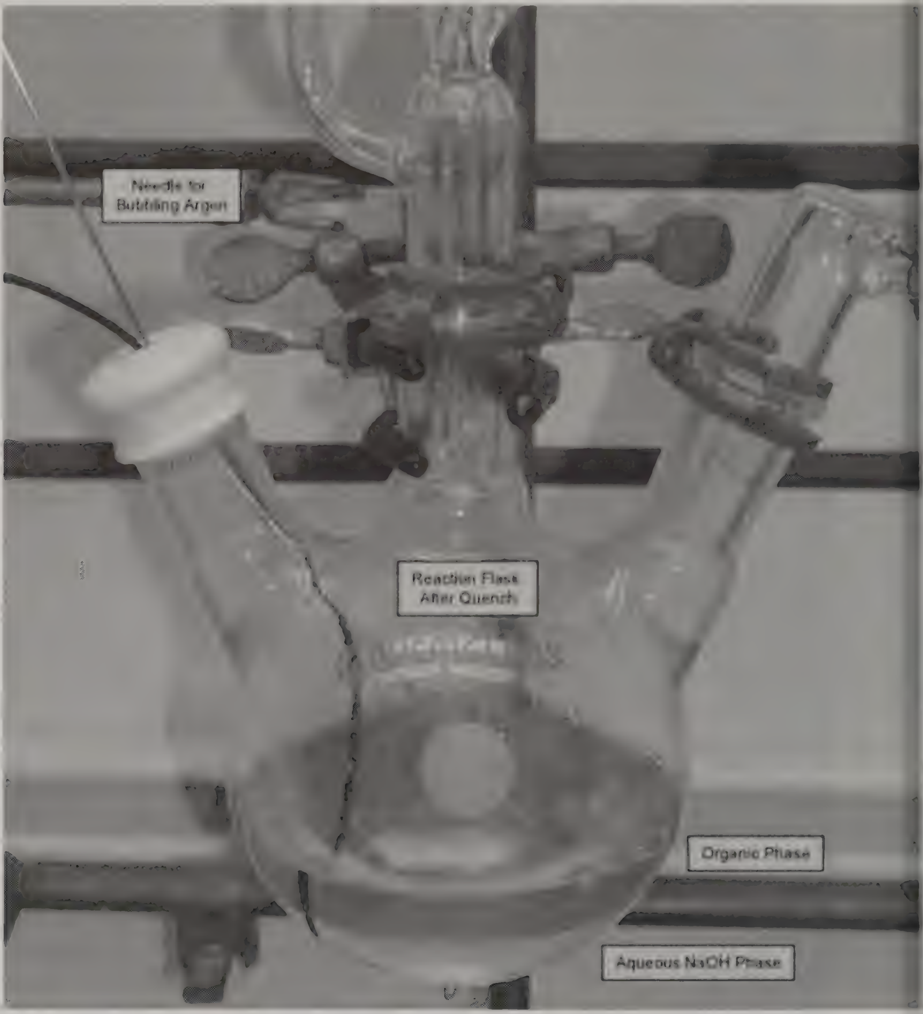


Figure 3: Filtration of Secondary Phosphine Solution

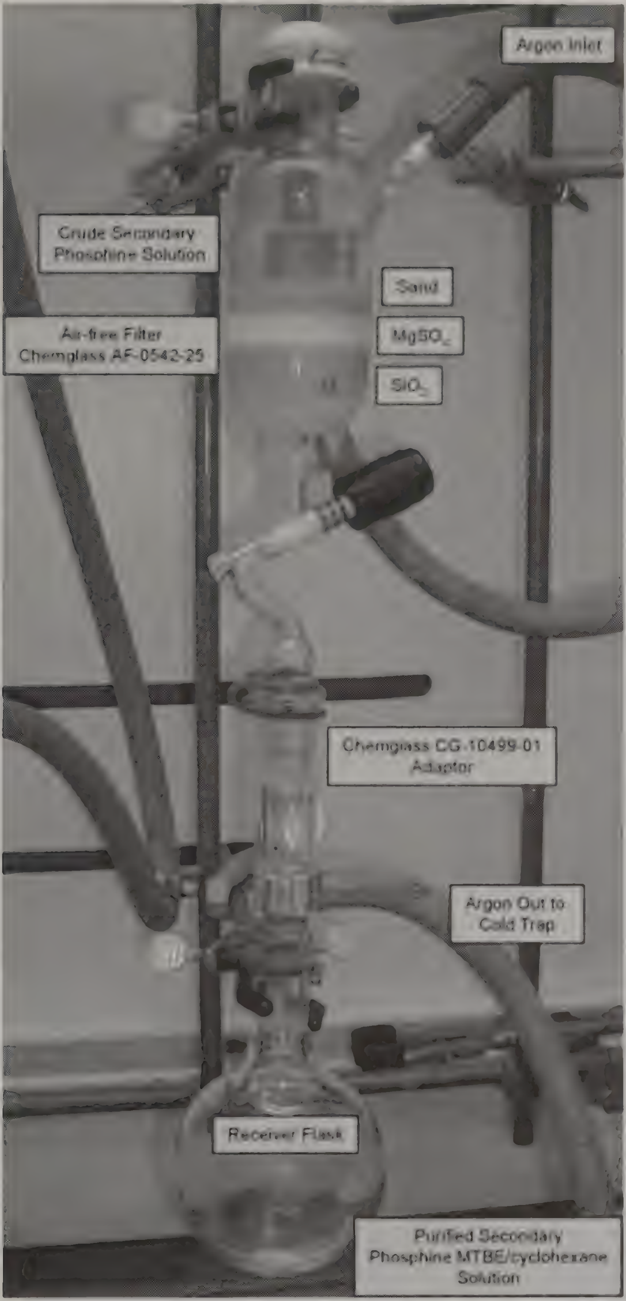

Argon Inlet
Crude Secondary Phosphine Solution
Sand
Air-free Filter Chemglass AF-0542-25
$MgSO_4$
SiO_2
Chemglass CG-10499-01 Adaptor
Argon Out to Cold Trap
Receiver Flask
Purified Secondary Phosphine MTBE/cyclohexane Solution

Figure 4: Concentration of Purified Secondary Phosphine

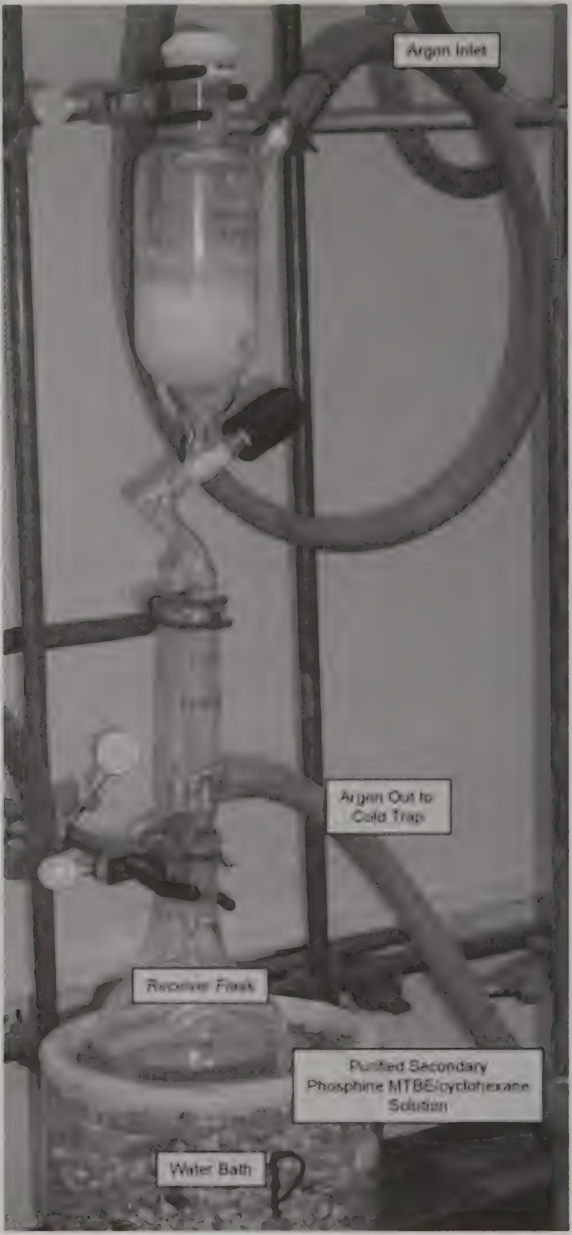


Figure 5: Concentrated Secondary Phosphine

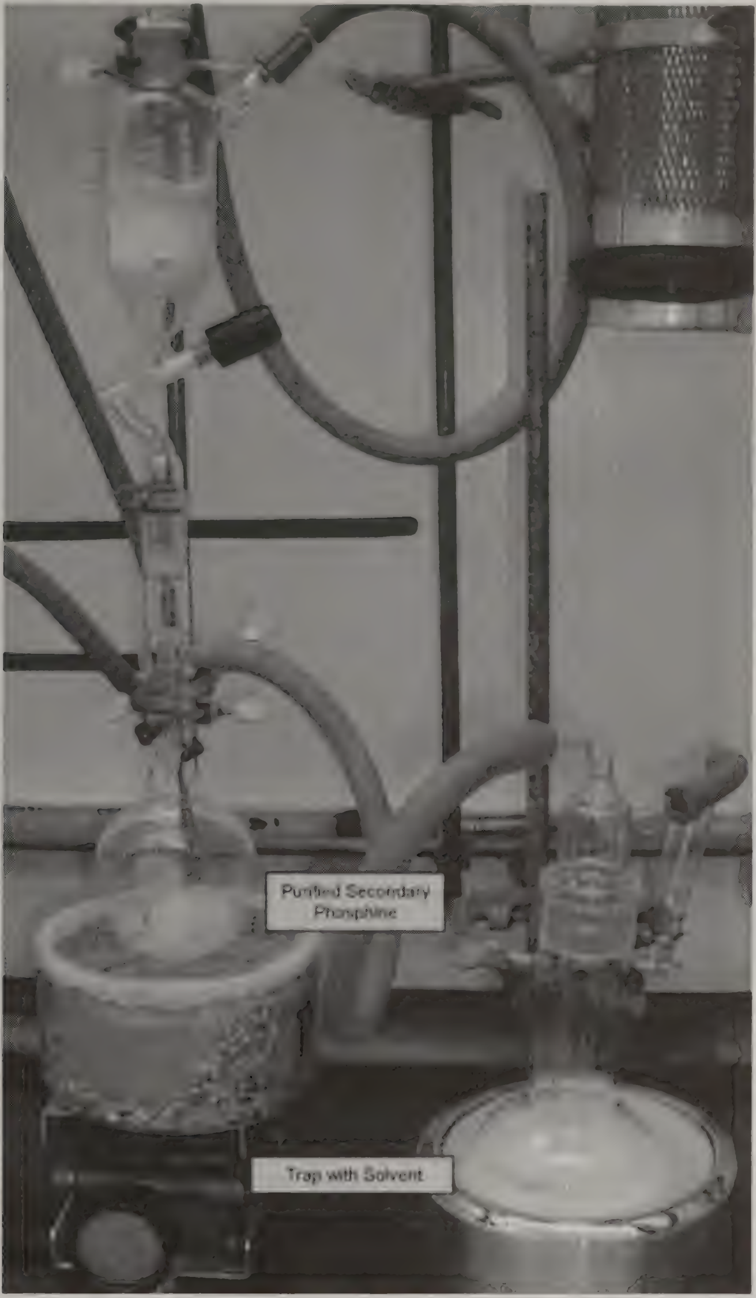
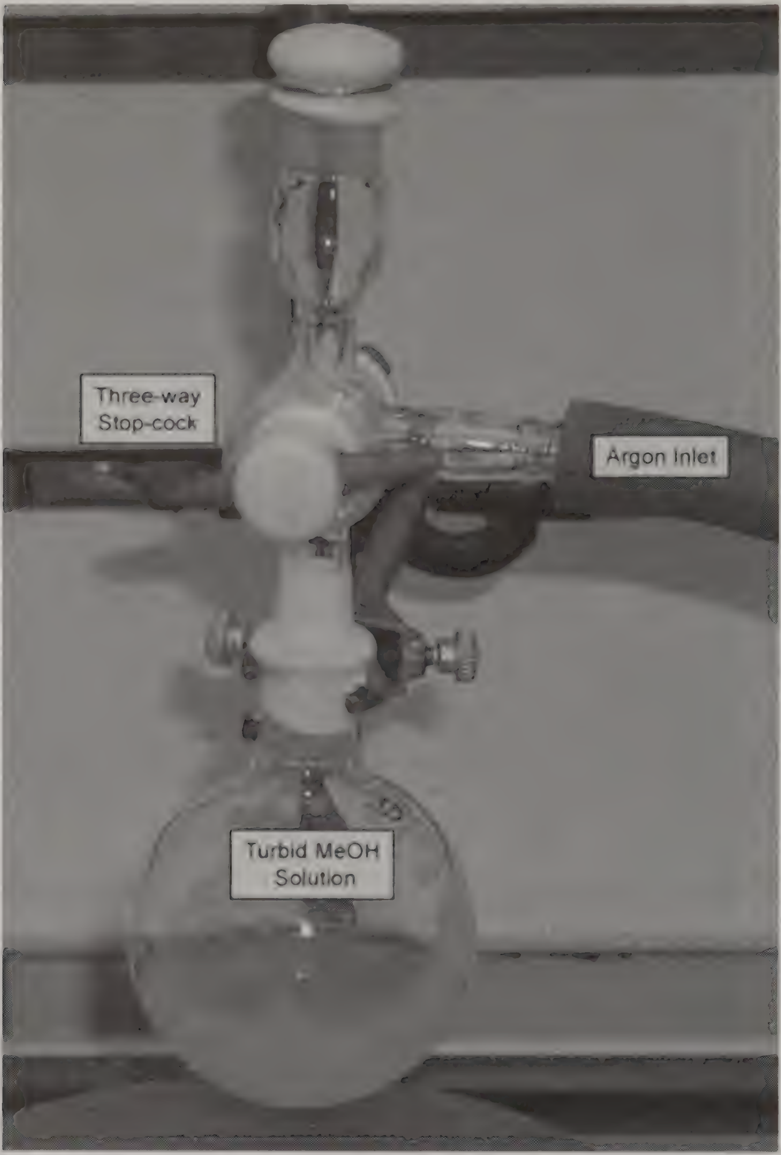


Figure 6: Recrystalization of Secondary Phosphine



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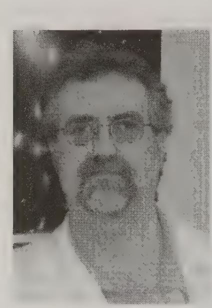
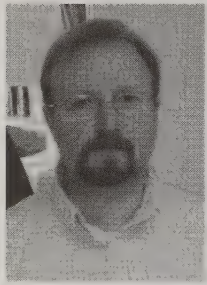
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Bis[3,5-bis(trifluoromethyl)phenyl]-phosphine oxide (15979-14-3)
3,5-Bis(trifluoromethyl)bromobenzene: Benzene, 1-bromo-3,5-bis(trifluoromethyl)-; (328-70-1)
Diethyl phosphite: Phosphonic acid, diethyl ester : (762-04-9)
Bis[3,5-bis(trifluoromethyl)phenyl]phosphine (166172-69-6)

DIBAL: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)



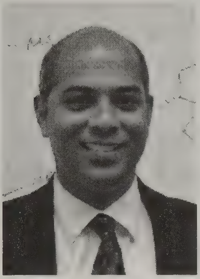
Dr. Carl A. Busacca obtained his undergraduate degree from North Carolina State University. After three years with Union Carbide in North Carolina, he attended graduate school at Colorado State University, where he received his Ph.D. with Professor A.I. Meyers in 1989. He joined Sterling Winthrop in Rensselaer, New York. In 1994, Dr. Busacca joined the Department of Chemical Development at Boehringer-Ingelheim, where he is currently Distinguished Scientist. His research interests include the design of convergent chemical processes, the use of NMR in studying reaction mechanisms, asymmetric catalysis and the development of new organophosphorus chemistry.



Jon C. Lorenz received a B.A. degree in Chemistry from Whitman College, Walla Walla, WA in 1995. He then joined the Peace Corps and taught science in the North West Province of Cameroon. He then began his graduate studies at Colorado State University, where he received a Ph.D. in organic chemistry under the guidance of Professor Yian Shi in 2002. Subsequently, he joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT where he is currently a Principal Scientist. His research interests include the development and application of catalytic asymmetric reactions, and the many facets of process development.

Paul S. Sabila was born in 1976 in Trans-Nzoia, Kenya. He completed his undergraduate studies at the University of Nairobi in 1999. He then joined the laboratory of Dr. Amy R. Howell at the University of Connecticut where he graduated with his Ph.D. in 2006. He also did an internship at Boehringer-Ingelheim Pharmaceuticals under the supervision of Dr. Carl Busacca. He is currently pursuing postdoctoral work in the laboratory of Dr. Dennis L. Wright, Department of Medicinal Chemistry, University of Connecticut.

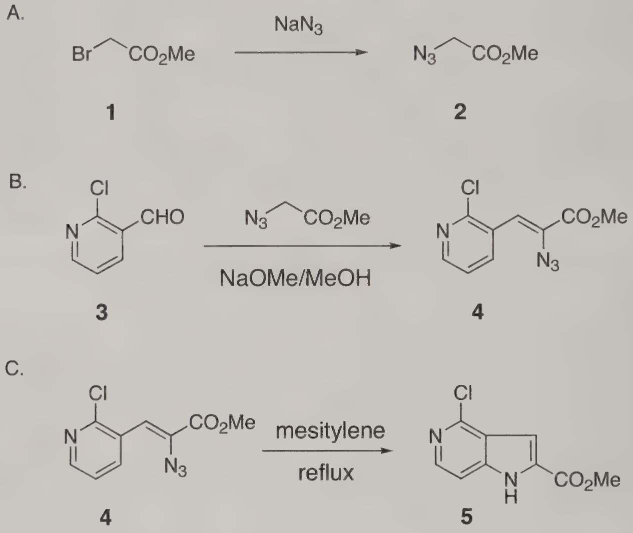
Dr. Nizar Haddad was born and raised in Israel. He received his B.A. degree in 1984 and his D.Sc. degree in chemistry from the Technion, Israel Institute of Technology with Professor D. Becker in 1988. After postdoctoral research at the University of Chicago with Professor J. D. Winkler and additional postdoctoral work at Harvard University with Professor Y. Kishi, he joined the faculty in the Chemistry Department at the Technion, Israel in 1991. Following a one-year sabbatical leave with Professor K. C. Nicolaou at the Scripps Research Institute, he joined Boehringer Ingelheim Pharm. Inc. in 1998 where he is currently Senior Principal Scientist.



Dr. Chris H. Senanayake obtained his Ph.D. at Wayne State University in 1987 where he worked on the total synthesis of complex natural products. He then undertook a postdoctoral fellow with Professor Carl R. Johnson and worked on the total synthesis of polyol systems such as amphotericin B and compactin analogous. He joined the Merck Process Research Group in 1990 as a Senior Research Chemist. In 1996, he joined Sepracor, Inc. as Director of Chemical Process Research. He was appointed as Executive Director of Chemical Process Research in 2001. In 2002, he joined Boehringer Ingelheim Pharmaceuticals, Inc. as Director of Chemical Process Research. In 2005, he was appointed as VP, Chemical Development.

Chris Regens was born and raised in Illinois and received his B.A. degree in Chemistry from Lake Forest College, where he performed undergraduate research with Professor William Martin. In 2003, he began his graduate studies at the University of Illinois at Urbana Champaign, under the guidance of Professor Scott Denmark. His research focuses on the application of silicon-based cross-coupling reaction for the total synthesis of complex natural products, which has recently culminated in the total synthesis of papulacandin D.

PREPARATION OF SUBSTITUTED 5-AZAINDOLES: METHYL 4-CHLORO-1*H*-PYRROLO[3,2-*C*]PYRIDINE-2-CARBOXYLATE



Submitted by Patrick Roy[1], Michel Boisvert, and Yves Leblanc.
Checked by Akiyoshi Kuramochi and Masakatsu Shibasaki.

1. Procedure

A. *Methyl azidoacetate* (**2**). *This reaction should be performed behind a safety shield.* To a solution of methyl bromoacetate (**1**) (51.5 mL, 0.528 mol) in MeOH (86 mL) in a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, reflux condenser, a drying tube, a septum through which is passed a metal temperature probe and a 20 °C water bath is added a slurry of sodium azide (42.3 g, 0.649 mol, 1.23 equiv) in H_2O (40 mL) via a funnel in one portion. The residual sodium azide is rinsed into the round-bottomed flask with water (2 x 6 mL). The suspension is stirred for 20 min in the water bath and a mild exotherm occurs (Note 2). The solution is then brought to gentle reflux with a heating mantle for 2 h. After cooling to room temperature, the solvent is removed carefully on the rotary evaporator (40 mmHg, 25 °C water bath), as the heterogeneous mixture has a tendency to bump. The residue is partitioned between Et_2O (100 mL) and H_2O (100

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mL), transferred to a separatory funnel and the aqueous phase is further extracted with of Et_2O (3 x 30 mL). The combined organic layer is dried with $MgSO_4$, filtered, and evaporated to give methyl azidoacetate (53.9–54.5 g, 89–90%) as a slightly yellow oil.

B. *Methyl (2Z)-2-azido-3-(2-chloropyridin-3-yl)acrylate* (**4**). *This reaction should be performed behind a safety shield.* A 2-L three-necked, round-bottomed flask (24/40 ground glass joints) is fitted with a drying tube, a 125-mL addition funnel, a magnetic stir bar (Note 3), and a septum through which is passed a metal temperature probe. To the flask is added 2-chloro-3-pyridine carboxaldehyde (20.0 g, 141 mmol) (Note 1), MeOH (200 mL), and methyl azidoacetate (32 mL, 349 mmol, 2.5 equiv) (Note 4). A slightly positive pressure of nitrogen is placed on the system via a needle through the septum. The flask is placed in an acetone bath, and dry ice is added slowly to the bath until the internal temperature reaches –10 to –12 °C (Note 5). At that point, a 25% solution of NaOMe in MeOH (80 mL, 4.37 M, 349 mmol, 2.5 equiv) is slowly added using the addition funnel over a period of 25 to 30 min. Dry ice is occasionally added to the cold bath during this time to maintain the internal temperature at approximately –9 to –12 °C. The reaction color changes from clear pale brown to cloudy orange/yellow as the addition proceeds, and mild bubbling is noted. When the addition is completed, the mixture is stirred an additional 15 min at –10 °C. The flask is then transferred to an ice bath, and stirring is continued for 2.5 h, during which time the internal temperature rises to 1.5 to 2 °C (Note 6). A tan-colored precipitate gradually forms (product), and slow bubbling is observed. The reaction is then placed in an ice bath in a 4 °C cold room, and is stirred overnight (16 h) with the drying tube in place. The flask is covered in aluminum foil to exclude light. The next morning, a 4-L Erlenmeyer flask is placed in an ice bath and the flask is then charged with 500 g of ice and 1.5 L of saturated NH_4Cl solution. A stir bar is transferred to the Erlenmeyer flask, and the tan-colored suspension is poured onto the stirring mixture over approximately 20 sec. The reaction flask is rinsed with 3 x 50 mL of ice water to ensure that any remaining solid is transferred. The final pH of the suspension is approximately 7.5. After stirring for an additional 5 min, the product is collected on a 12-cm Büchner funnel using a standard vacuum filtration setup, washing with ice-cold water (3 x 100 mL) (Note 7). The tan-colored solid is air-dried for 10 min on the Büchner funnel under suction from an aspirator, and is then transferred to a 1-L single-necked round-bottomed flask and placed under high vacuum for 30 min. Dichloromethane

(250 mL) is then added to dissolve the product, and $MgSO_4$ (approximately 3–4 g) is added to dry the solution. The pale brown solution is filtered through a 2-cm thick pad of silica gel 60 on a 4-cm sintered glass funnel, which removes some dark brown baseline material. The pale yellow solution is concentrated to dryness on the rotary-evaporator (approximately 15 mmHg) at 25 °C to give the product as a pale yellow solid (17.7–18.8 g, 53–56%) (Note 8).

C. *Methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate* (**5**). *This reaction should be performed behind a safety shield.* The product (**4**) from Step B (17.7 g, 74.2 mmol) is suspended in 740 mL of mesitylene (0.1 M) in a 2–L, single-necked round-bottomed flask equipped with a magnetic stir bar and a reflux condenser with a drying tube. The reaction mixture is stirred while being heated in an oil bath at 185 °C (Note 9), and after approximately 3 min, the starting material dissolves. At 5 min, bubbling occurs for several min as N_2 is extruded from **4**. After 30 min, the mixture is gently refluxing, which is maintained for 1 h. The clear deep yellow solution is then allowed to stand at room temperature for 1 h, during which time a thick pale yellow precipitate forms. After cooling to 0 °C for 1 h, the product is collected on a 12–cm Büchner funnel, washing with 4 x 50 mL of cold hexanes. The solid is then suspended with vigorous stirring overnight in 200 mL of EtOAc:hexanes (1:20, vol/vol). The product is then collected on a 12–cm Büchner funnel and washed with 2 x 50 mL of hexanes to give a pale yellow solid (10.7 g, 69%) (Note 10).

2. Notes

1. Methyl bromoacetate (97% purity) was obtained from Lancaster Synthesis. Sodium azide (>99.5% purity), 2-chloro-3-pyridine carboxaldehyde (97% purity), 25% NaOMe/MeOH and mesitylene (98% purity) were obtained from the Aldrich Chemical Co. MeOH was Optima D.I.G. grade (4 L, 0.07% H_2O) from Fisher.

2. A mild exotherm to approximately 45 °C was observed, although this exothermic behaviour never showed any sign of loss of control. Differential scanning calorimetry indicated an endotherm at 58 °C. This reaction was carried out at this scale or greater without incident. The characterization of **2** is as follows: ^{1}H NMR (500 MHz, acetone-d_6) δ: 3.77 (s, 3 H), 4.04 (s, 2 H). ^{13}C NMR (126 MHz, acetone-d_6) δ: 50.47. 52.64, 169.87; IR (neat): cm^{-1} 2108, 1751.

3. Mechanical stirring was not necessary, although for other substrates such as 2-methoxy-3-pyridine carboxaldehyde[2] the reaction became a thick paste overnight at 0 °C. This thickening, however, did not appear to affect the yield.

4. In the original papers using methyl azidoacetate for the condensation step (Monatshefte Chemie **1969**, 100(5) 1599), the authors used 4 equivalents of the reagent, which was reduced to 2.5 equivalents in the above procedure. The excess was felt to be necessary since the reagent slowly decomposed with time, as indicated by the gentle bubbling during the condensation step.

5. The addition was also carried out successfully at –30 °C for this substrate. However, for 2,4-dichloro-3-pyridine carboxaldehyde[2] addition at –30 °C followed by warming to 0 °C resulted in an exotherm to >12 °C, which led to the mixture frothing out of the flask. No product was recovered. As a *precaution* when carrying out the reaction, the flaps on the septa are not folded down in order to minimize problems arising from any build-up of pressure in the event of an exotherm.

6. If a non-insulated container such as a plastic bowl is used for the ice bath, care must be taken to maintain enough ice to prevent the internal temperature from rising too high. Internal temperatures of 4 °C have been noted with ice floating in water in the bath.

7. The filtration can require 15–20 min due to the fine nature of the crystals. A larger Büchner funnel reduces this filtration time. The aqueous/MeOH filtrate soon turned a dark red after filtration.

8. The product was best stored in the refrigerator or freezer, covered in aluminum foil, although we noted no change in the NMR spectra after several days at room temperature. Depending on the substitution pattern on the pyridine ring, the intermediate **4** gradually darkened over several weeks/months in the refrigerator. The material was repurified by dissolution in CH_2Cl_2 and filtration through a small plug of silica gel to remove baseline material. Differential scanning calorimetry of this material indicated that an exotherm occurred at approximately 120 ºC. The characterization for **4** is as follows: mp = 107–109 ºC (dec, gas bubbles); ^1H NMR (500 MHz, $CDCl_3$) δ: 3.93 (s, 3 H). 7.16 (s, 1 H), 7.26 (dd, J = 7.9, 4.8 Hz, 1 H), 8.29 (dd, J = 4.8, 1.7 Hz, 1 H), 8.50 (dd, J = 7.9, 1.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 53.54, 118.65, 122.50, 128.29, 129.22, 139.48, 149.35, 151.33, 151.33. IR (KBr): cm^{-1} 2129, 1708. MS (ESI+): *m/z* 260.7 (M+1) (100%)

9. The reaction was also carried out through use of a heating mantle, but some dark brown solid material formed on the walls of the flask. The yield was not greatly affected.

10. The characterization for **5** prior to chromatography was as follows: mp = 210–212 ºC (dec); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.91 (s, 3 H), 7.19 (s, 1 H), 7.43 (d, J = 5.8 Hz, 1 H), 8.09 (d, J = 5.8 Hz, 1 H), 12.77 (br s, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 52.29, 105.97, 107.87, 122.08, 129.15, 141.51, 141.85, 144.23, 160.81; IR (KBr): cm^{-1} 1718. MS (ESI+) *m/z* 210.8 (M+H) (58%), M+Na 232.7 (100%). Anal. Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.31; H, 3.41; N, 13.11. Although further purification was not necessary, the product was purified on small scale (100 mg) by flash chromatography on silica gel 60 (EMD), eluting with 30 % EtOAc/hexanes. The crude solution in mesitylene was applied directly to the column before the product precipitated.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes the preparation of methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate, a 4-Cl-5-azaindole, via thermolysis of an intermediate azidopyridine acrylate (Hemetsberger-Knittel reaction).[3] The product is isosteric with the analogous indole template, and represents an interesting scaffold from the point of view of medicinal chemistry. Furthermore, with four sites available for selective functionalization, one could envisage a wide range of chemical diversity in the construction of libraries based on this core structure. Table 1 shows the results obtained for the preparation of a variety of 5, 6, and 7-azaindoles. Procedure A (100 mg of pyridine acrylate at 0.1 M) involves bulb-to-bulb distillation of the mesitylene followed by chromatography. Procedure B is used for amounts greater than 500 mg of the pyridine acrylate and is performed as described in the current preparation. Procedure C is for the synthesis of 6-azaindoles (entries 13 and 14) and involves adding the pyridine acrylate to a refluxing solution of decalin (190 ºC) at a concentration of 2 g/ 500 mL and refluxing 10 min before cooling and filtering.

Of the unsubstituted pyridine acrylates (entries 1-3), only the 7-azaindole was obtained, albeit in low yield (25%). For the two 6-azaindole precursors listed in entries 13 and 14, decomposition/poor yields were observed upon thermolysis at 160 ºC, whereas use of refluxing decalin gave acceptable yields (44%, 51%). There appears to be a minimum threshold below which the desired cyclization does not readily take place for these substrates. The best results were obtained with 5-azaindoles (entries 4-12). The thermolysis proceeds smoothly at 160 ºC with halogen, ether, thioether, methylsulfone, and alkyl substituents on the pyridine ring to give good yields (66–93%) with the exception of the methoxychloro-substituted entry 12 (32%).

Table 1. Thermolysis of 2-Azido-3-pyridine Acrylates

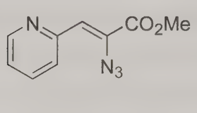
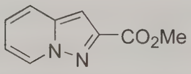
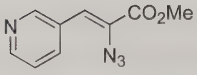
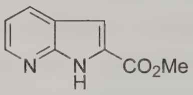
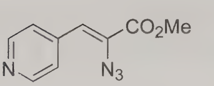
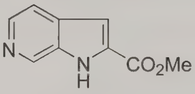
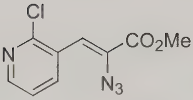
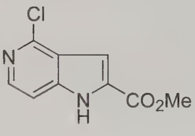
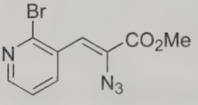
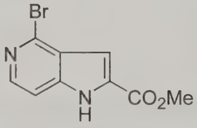
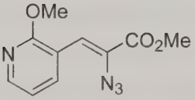
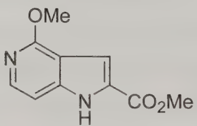
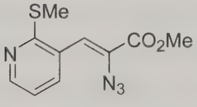
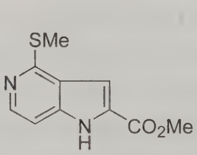
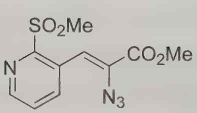
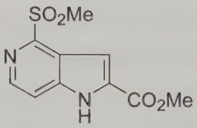
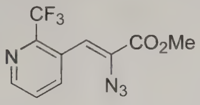
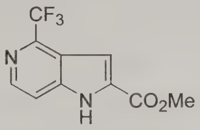
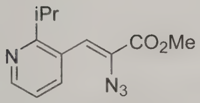
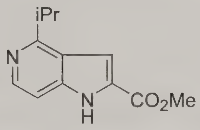
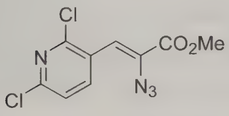
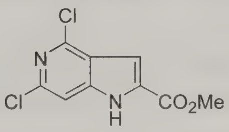
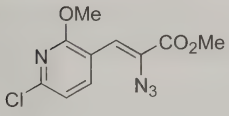
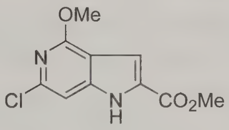
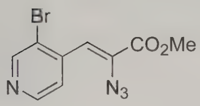
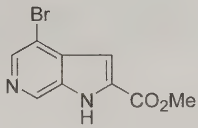
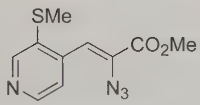
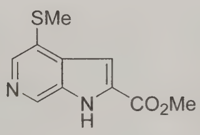
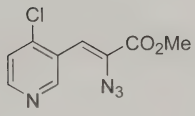
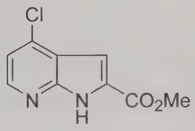
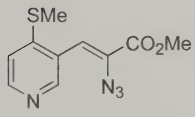
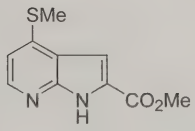
Entry	Azidopyridine acrylate	Procedure	Product	Yield(%)
1		B		67
2		B		25
3		B		0
4		B		72
5		A		78
6		A		93
7		A		84
8		A		69

Table 1. (continued) Thermolysis of 2-Azido-3-pyridine Acrylates

Entry	Azidopyridine acrylate	Procedure	Product	Yield(%)
9		B		66
10		B		75
11		A		77
12		A		32
13		C		44
14		C		51
15		A		40
16		B		56

1. Merck Frosst Centre for Therapeutic Research, C.P. 1005, Pointe Claire-Dorval , Québec H9R 4P8, Canada.
2. Roy, P.J.; Dufresne, C.; Lachance, N.; Leclerc, J-P.; Boisvert, M.; Wang, Z.; Leblanc, Y. *Synthesis* **2005**, *16*, 2751-2757.
3. a) Hemtsberger, H.; Knittel, D.; Wiedmann, H. *Monatshefte Chemie* **1970**, *101*, 161-165. For references on the preparation of azaindoles via this reaction, see b) Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41,* 4777-4780 and c) Lomberget, T.; Radix, S.; Barret, R. *Synlett* **2005**, *13*, 2080-2082.

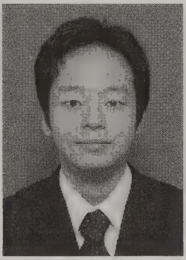
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Methyl azidoacetate: Acetic acid, azido-, methyl ester; (1816-92-8)
Methyl bromoacetate: Acetic acid, bromo-, methyl ester; (96-32-2)
Sodium azide; (26628-22-8)
Methyl (2*Z*)-2-azido-3-(2-chloropyridin-3-yl)acrylate: 2-Propenoic acid, 2-azido-3-(2-chloro-3-pyridinyl)-, methyl ester; (688357-18-8)
2-Chloro-3-pyridinecarboxaldehyde; (36404-88-3)
Methyl 4-chloro-1*H*-pyrrolo[3,2-c]pyridine-2-carboxylate: 1*H*-Pyrrolo[3,2-c]pyridine-2-carboxylic acid, 4-chloro-, methyl ester; (688357-19-9)
Mesitylene: 1,2,3-Trimethylbenzene; (108-67-8)

Patrick Roy was born in Deep River, Canada, in 1960. After completing a Co-operative Chemistry B.Sc. at the University of Waterloo in 1984 with an emphasis on organic chemistry, he joined a custom synthesis group in the fine chemical industry. In 1985 he resumed his studies, in Prof. Hanessian's group at Université de Montréal where he obtained his M.Sc. During this time he completed a formal synthesis of dihydromevinolin. He joined Merck Frosst Canada Inc. in 1988 where he is currently a Research Associate.

Michel Boisvert was born in 1983 in Ottawa, Canada. He started his undergraduate studies at University of Sherbrooke in 2002 and received a B.S. degree in Chemistry in 2006. In 2006, Michel began his M.Sc. studies at Université de Montréal and joined the research group of Professor Stephen Hanessian. Since starting his graduate studies, his research has focused on the total synthesis of Calyciphylline B, a natural product isolated from the leaves of Daphniphyllum calycinum.

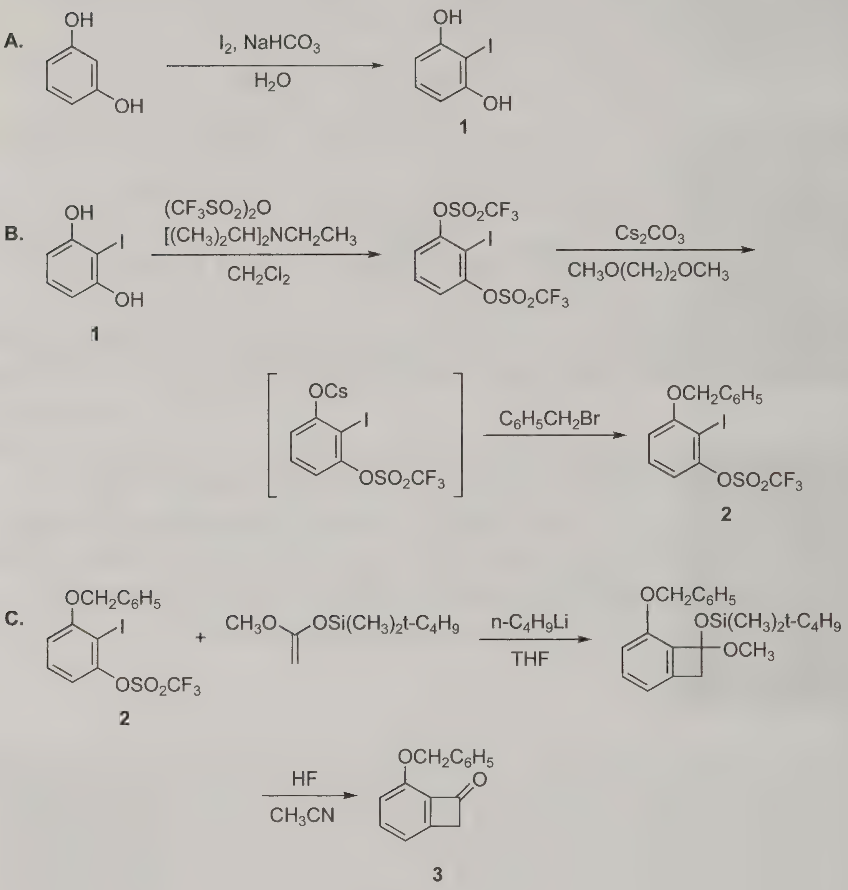
Yves Leblanc was born in 1959 in Montreal, Canada. After undergraduate studies at Université de Montréal from 1978-1981, he joined the group of Prof. Stephen Hanessian where he obtained his M.Sc. degree in 1982. His work there was focused on phosphorus chemistry including diazaphospholanes and asymmetric olefination and alkylation. In February 1983 he joined Merck Frosst Canada Inc., where he is currently a Senior Research Fellow. During his 24 year career he has been involved in several projects, including leucotriene synthesis, LTD4 antagonist, and cyclooxygenase programs.



Akiyoshi Kuramochi was born in 1981 in Yokohama, Japan. He received B.S. in 2003 and M.S. in 2005 from The University of Tokyo. Presently, he is pursuing his Ph.D. degree at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, under the guidance of Professor Masakatsu Shibasaki. His research interests are in the area of total synthesis of complex natural compounds.

PREPARATION OF BENZOCYCLOBUTENONE DERIVATIVES BASED ON AN EFFICIENT GENERATION OF BENZYNES

(Bicyclo[4.2.0]octa-1,3,5-trien-7-one, 5-(phenylmethoxy)-)



Submitted by Shin-ichiro Tsujiyama and Keisuke Suzuki.[1a]
Checked by David B. Guthrie, Heather M. Gibney and Dennis P. Curran.[1b]

1. Procedure

Caution! Iodine, trifluoromethanesulfonic anhydride, benzyl bromide and hydrofluoric acid are toxic and/or corrosive reagents and should be *handled in a well-ventilated hood. Calcium gluconate gel should be present for first aid in case of accidental exposure of skin to HF.*

A. 2-Iodoresorcinol (**1**) (Note 1). A 250-mL, one-necked, round-bottomed flask equipped with a large, elliptical stir bar and open to the atmosphere is charged with distilled water (46 mL), resorcinol (7.27 g, 66.0 mmol) and iodine (17.92 g, 70.6 mmol), and then placed in an ice-water bath (Note 2). To this open flask is slowly added sodium bicarbonate (6.16 g, 73.3 mmol) in portions by spatula over 5 min at 0 °C with vigorous stirring (Notes 2, 3). During the addition, vigorous gas evolution (carbon dioxide) is observed. The ice bath is removed and the mixture is allowed to warm to room temperature over 20 min, then stirred for a further 10 min, during which time it becomes a brown slurry (Note 4). The products are extracted with ethyl acetate (3 x 50 mL). The combined organic extract is successively washed with 10% aqueous sodium thiosulfate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (Note 5). The solid residue is triturated in chloroform (20 mL) for 10 min at –10 °C (ice/ethanol bath), filtered, and washed with cold (–10 °C) chloroform (20 mL) to give 9.12 g (58%) of 2-iodoresorcinol (**1**) as a cream-colored solid. The filtrate is concentrated under reduced pressure, and the residue is triturated in chloroform (7 mL) for 30 min at –10 °C, filtered, and washed with 5 mL of chloroform (0 °C) to give an additional 1.18 g (8%, 66% combined yield) of 2-iodoresorcinol (**1**) as a cream-colored solid. (Notes 6, 7, 8, 9).

B. 3-Benzyloxy-2-iodophenyl trifluoromethanesulfonate (**2**). An oven-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon gas inlet and a rubber septum is charged with 2-iodoresorcinol (**1**) (11.49 g, 48.7 mmol) and dichloromethane (115 mL) (Note 10), and the mixture is cooled to –78 °C with a dry ice–acetone bath. *N,N*-Diisopropylethylamine (20.4 mL, 117 mmol) is added by syringe. Then trifluoromethanesulfonic anhydride (18.0 mL, 107 mmol) is slowly added over 15 min by syringe pump while maintaining the reaction mixture at –78 °C (Note 11). After stirring for 10 min at –78 °C, the reaction mixture is warmed to 0 °C by replacing the dry ice bath with an ice water bath, and stirred for 1 h (Note 12). The reaction is quenched by the slow addition of water (100 mL, added over 10 min), and the products are extracted with dichloromethane (2 x 50 mL). The combined organic extract is successively washed with saturated aqueous sodium bicarbonate solution (2 x 50 mL) and brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue is dissolved in diethyl ether (50 mL) and hexanes (50 mL), and then silica gel (12.0 g) (Note 13) is added. After stirring for 30 min at room temperature, the mixture is filtered, and the silica cake is washed with a mixture of diethyl ether (75 mL) and hexanes (75 mL). The filtrate is concentrated under reduced pressure and vacuum dried to give 24.31–24.33 g of crude 2-iodoresorcinol bis(trifluoromethanesulfonate) as a dark brown oil. This is used directly for the next step without further purification.

A 500-mL, one-necked round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser attached to an inert atmosphere inlet is placed under argon and charged with the crude 2-iodoresorcinol bis(trifluoromethanesulfonate) (24.3 g), 1,2-dimethoxyethane (100 mL) and cesium carbonate (19.06 g, 58.5 mmol) (Note 14). The resulting mixture is stirred for 4 h in an 80 °C oil bath (Note 15). After cooling to room temperature, benzyl bromide (6.96 mL, 58.5 mmol) (Note 16) is added via syringe over 2 min, then the reaction mixture is stirred for 5 h at room temperature (Note 17). Diethylamine (2.5 mL, 24.4 mmol) (Note 18) is added via syringe through the top of the condenser, and the mixture is stirred for 1 h at room temperature. The mixture is cooled in an ice bath and 1 M hydrochloric acid (200 mL) is added, dropwise at first, then more rapidly as the exotherm subsides. The mixture is warmed to room temperature and the products are extracted with ethyl acetate (3 x 100 mL). The combined organic extract is successively washed with brine (2 x 100 mL), saturated aqueous sodium bicarbonate (2 x 100 mL), and brine (2 x 100 mL). The extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 26.3–26.5 g of a brown oil. The residue is purified by column chromatography on silica gel (Note 19) to give 16.5–17.4 g (74–78%) of 3-benzyloxy-2-iodophenyl trifluoromethanesulfonate (**2**) as yellow crystals (Note 20), which are used directly for the next step.

C. 5-Benzyloxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**3**). An oven-dried, single-necked 500-mL round-bottomed flask equipped with a magnetic stirring bar, an argon inlet and a rubber septum is charged with 3-benzyloxy-2-iodophenyl trifluoromethanesulfonate (**2**) (12.6 g, 27.5 mmol). The flask is flushed with argon, tetrahydrofuran (76 mL) (Note 21) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (8.99 mL, 41.2 mmol) (Note 21) are added by syringe, and the mixture is cooled to –78 °C (bath temperature) with a dry ice–acetone bath. A solution of butyllithium in hexanes (20.63 mL of a 1.6 M solution, 33.0 mmol) (Note 22) is added to the reaction mixture over 20 min via syringe pump using a needle inserted through the septum. The reaction mixture is further stirred for 10 min at –78 °C (Note 23), then water (2 mL) is added dropwise. After warming to room temperature, water (100 mL) is added, and the products are extracted with ethyl acetate (3 x 100 mL). The combined organic extract is successively washed with brine (3 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 10.5–10.8 g of crude 5-benzyloxy-7-*tert*-butyldimethylsilyloxy-7-methoxy-bicyclo-[4.2.0]octa-1,3,5-triene as a brown oil. This is used directly for the next step without further purification.

A 250-mL, three-necked, round-bottomed flask (Note 24) equipped with a magnetic stirring bar, an addition funnel, a stopper and an argon inlet is charged with 5-benzyloxy- 7-*tert*-butyldimethylsilyloxy-7-methoxybicyclo[4.2.0]octa-1,3,5-triene (10.5–10.8 g), acetonitrile (82 mL), and the mixture is cooled to 0 °C in an ice-water bath. Aqueous hydrofluoric acid (48%, 12.5 mL, 345 mmol) (Note 25) is slowly added during 2 min via addition funnel. The mixture is warmed to room temperature over 20 min, then stirred an additional 20 min (Note 26). The reaction mixture is carefully poured into saturated aqueous sodium bicarbonate solution (300 mL) (Note 27), and the products are extracted with ethyl acetate (3 x 100 mL). The combined organic extract is successively washed with saturated aqueous sodium bicarbonate solution (3 x 100 mL) and brine (3 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 6.24–7.08 g of a yellow solid. The solid is taken up in hot hexanes (40 mL warmed to 60 °C) and the resulting mixture is quickly filtered to remove small amounts of insoluble brown solid. Cooling to 0 °C in an ice bath followed by filtration of the precipitate and washing with cold hexanes gives 3.72–4.34 g (60–70%) of 5-benzyloxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**3**) as a white solid (Notes 28, 29).

2. Notes

1. The iodination process was based on the procedure by Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1991**, *45*, 539.

2. The submitters used distilled water, iodine and sodium bicarbonate

purchased from Kanto Chemical Co., Inc. Resorcinol was purchased from Tokyo Kasei Kogyo Co., Inc. The checkers used Aldrich HPLC grade distilled water. Sodium bicarbonate was purchased from EMD, resorcinol from Lancaster (99%), and iodine from Aldrich or Fisher (ACS reagent grade, >99.8%). All reagents were used without further purification.

3. The checkers used an elliptical stir bar shaped like an American football, 32 mm long and 17 mm in diameter at the widest point. The submitters used a mechanical stirrer. Rapid stirring was essential for the success of the reaction, and a good vortex was required to prevent a foam from forming on the surface of the mixture during the addition of bicarbonate. When the stirring was not efficient, less 2-iodoresorcinol was formed along with increased amounts of 4-iodoresorcinol, 2,4-diiodoresorcinol and unreacted resorcinol. Sodium bicarbonate was added every few seconds in portions of about 55–65 mg by spatula.

4. Reaction progress was monitored by TLC analysis on Merck silica gel 60 F254 plates, visualized by a 254-nm UV lamp and stained with an aqueous solution of phosphomolybdic acid. TLC analysis showed the formation of 2-iodoresorcinol (**1**) (3/2 hexanes/ethyl acetate, R_f = 0.48). The side products (4-iodoresorcinol and 2,4-diidoresorcinol) had similar R_f values to the target product, while the R_f of resorcinol was 0.28.

5. The residue usually solidified spontaneously at this point. If not, chloroform (20 mL) was added and the mixture was again evaporated.

6. The submitters obtained a first crop from trituration of 9.49 g (61%) and a second crop of 2.18 g (14%) for a total yield of 2-iodoresorcinol (**1**) of 75%.

7. A reaction conducted at twice the indicated scale gave 21.86 g (70%) 2-iodoresorcinol (**1**) after two titrations (20.11 g, then 1.75 g).

8. The product was stored in a dark bottle at 5 °C because slow decomposition occurred on exposure to ambient light at room temperature.

9. Mp 99–101 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ: 6.46 (d, J = 8.1 Hz, 2 H), 7.00 (t, J = 8.1 Hz, 1 H), 8.83 (s, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ: 75.4, 107.1, 130.4, 158.8; IR (thin film, $CHCl_3$): 3456, 3363 (broad), 1593, 1582, 1491, 1458, 1304, 1278, 1250, 1185, 1159, 1022, 994, 784, 704 cm^{-1}; EIMS (*m/z*): M$^+$ 237 (6), 236 (100), 218 (23), 127 (16), 81 (13), 63 (8), 53 (17); HRMS (*m/z*): [M]$^+$ calcd for $C_6H_5IO_2$, 235.9334; found, 235.9333. Anal. calcd. for $C_6H_5IO_2$: C, 30.54; H, 2.14. Found: C, 30.27; H, 2.14.

10. Dichloromethane, purchased from Asahi Glass Co., Inc. or

Aldrich Chemical Co, was distilled from phosphorus pentoxide and calcium hydride (submitters) or dried by passing through an activated alumina column (checkers).

11. *N,N*-Diisopropylethylamine was purchased by the submitters from Tokyo Kasei Kogyo Co., Inc., and trifluoromethanesulfonic anhydride was donated from Central Glass Co., Inc. These reagents were used without further purification. The submitters purchased these chemicals from Aldrich Chemical Co. and redistilled the amine before use.

12. TLC analysis showed the formation of 2-iodoresorcinol bis(trifluoromethanesulfonate) (4/1 hexanes/ethyl acetate, $R_f = 0.57$).

13. Silica gel (60 Å, for column chromatography) was purchased from Kanto Chemical Co., Inc. (submitters) or Sorbent Technologies (60 Å, 230 x 400 mesh) (checkers).

14. 1,2-Dimethoxyethane was purchased from Tokyo Kasei Kogyo Co., Inc. (submitters) or J. T. Baker (checkers). Cesium carbonate (Reagent Plus, 99%) was purchased from Aldrich Chemical Co. These reagents were used without further purification.

15. TLC analysis showed the formation of 3-hydroxy-2-iodophenyl trifluoromethanesulfonate (4/1 hexanes/ethyl acetate, $R_f = 0.24$).

16. Benzyl bromide purchased from Tokyo Kasei Kogyo Co., Inc. (submitters) or Aldrich Chemical Co. (Reagent grade, 98%) (checkers) was used without further purification.

17. TLC analysis showed the formation of 3-benzyloxy-2-iodophenyl trifluoromethanesulfonate (**2**) (4/1 hexanes/ethyl acetate, $R_f = 0.45$).

18. Diethylamine was used to quench the excess benzyl bromide. Diethylamine was purchased from Kanto Chemical Co., Inc. (submitters) or Aldrich Chemical Co. (Reagent Plus, >99.5%) (checkers) and was used without further purification.

19. The product was taken up in 3/1 hexanes/ethyl acetate and stirred for 1 h. The organic solution was decanted from a small amount of dark brown solid directly onto the column. The chromatography was performed on 300 g of silica gel eluting with 10/1 hexanes/ethyl acetate.

20. Mp 86–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.21 (s, 2 H), 6.86 (d, $J = 8.1$ Hz, 1 H), 6.98 (d, $J = 8.4$ Hz, 1 H), 7.32–7.40 (m, 2 H), 7.40–7.48 (m, 2 H), 7.48–7.53 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 71.4, 83.3, 111.6, 114.3, 118.7 (q, $J_{C\text{-}F} = 318.8$ Hz), 126.9, 128.1, 128.6, 130.3, 135.6, 151.2, 159.4; IR (thin film, $CHCl_3$): 1589, 1450, 1425, 1273, 1224, 1209, 1139, 1056, 1024, 947, 850, 826, 732 cm^{-1}; EIMS (*m/z*): M$^+$ 459 (6), 458

(36), 382 (24), 368 (11), 367 (7), 249 (11), 197 (52), 107 (64), 92 (98), 79 (44), 69 (78), 65 (100); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{10}F_3IO_4S$, 457.9297; found, 457.9316. Anal. calcd. for $C_{14}H_{10}F_3IO_4S$: C, 36.70; H, 2.20. Found: C, 36.77; H, 2.19.

21. 1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene was obtained from Aldrich Chemical Co., Inc., and used without further purification. The submitters observed that distillation of 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene under argon did not result in increased product yield or purity. The submitters used tetrahydrofuran (dehydrated, stabilizer free) purchased from Tokyo Kasei Kogyo Co., Inc. without further purification. The checkers used THF from Aldrich Chemical Co. (99%, inhibitor free), which was dried by passing through activated alumina.

22. Butyllithium in hexanes was purchased from Kanto Chemical Co., Inc. (submitters) or Aldrich Chemical Co. (checkers).

23. TLC analysis showed consumption of starting material and formation of 5-benzyloxy-7-*tert*-butyldimethylsilyloxy-7-methoxybicyclo-[4.2.0]octa-1,3,5-triene (4/1 hexanes/ethyl acetate, $R_f = 0.74$).

24. The submitters and checkers used a glass vessel for this reaction, but the submitters reported that a polypropylene flask could also be used to avoid corrosion of the flask by hydrofluoric acid.

25. The submitters used acetonitrile and a 46% aqueous solution of hydrofluoric acid, purchased from Kanto Chemical Co., Inc. without further purification. The checkers used acetonitrile from J. T. Baker and 48% HF from Mallinckrodt.

26. TLC analysis showed the formation of 5-benzyloxybicyclo-[4.2.0]octa-1,3,5-trien-7-one (**3**) (4/1 hexanes/ethyl acetate: $R_f = 0.55$).

27. Vigorous evolution of carbon dioxide gas was observed.

28. Mp 80–81 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.95 (s, 2 H); 5.47 (s, 2 H), 6.90 (d, $J = 8.4$ Hz, 1 H), 7.06 (d, $J = 6.9$ Hz, 1 H), 7.30-7.43 (m, 3 H), 7.43-7.51 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.1, 73.8, 115.1, 116.3, 127.7, 128.0, 128.3, 132.4, 136.3, 137.6, 150.4, 152.1, 184.7; IR (thin film, $CHCl_3$): 3033, 2929, 1761, 1604, 1573, 71475, 1453, 1386, 1274, 1160, 1129, 1052, 787, 755 cm^{-1}; EIMS (*m/z*): M^+ 224 (20), 105 (6), 91 (100), 65 (13), 51 (14). HRMS (*m/z*): $[M]^+$ calcd for $C_{15}H_{12}O_2$: 224.0837; found: 224.0845. Anal. calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.36; H, 5.10.

29. The submitters obtained a second crop as follows. The filtrate was concentrated under reduced pressure to give 1.62 g of a yellowish solid,

which was recrystallized from hexanes (6 mL, at 60 °C followed by cooling down to 0 °C using an ice bath) to give the second crop of **3** (0.60 g, 10%). In the checkers' hands, the second crop product was about 90–95% pure according to ^{1}H NMR spectroscopy.

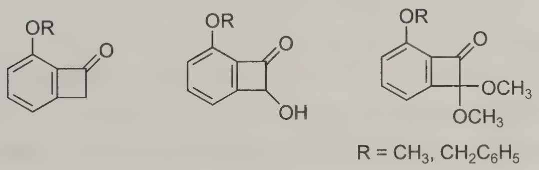
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Benzocyclobutenes have long attracted much attention due to their molecular structure, chemical reactivity and synthetic potential.[2] They have served as important building blocks for syntheses of various natural products by exploiting their unique reactivity. Due to their inherent strain, benzocyclobutenes are capable of isomerizing to quinodimethanes that can in turn be used to derive various polycyclic skeletons via Diels-Alder reactions or electrocyclizations. Described here is an effective procedure for the synthesis of highly oxygenated benzocyclobutenones, which have great synthetic potential, since a carbonyl group in the four-membered ring can serve as a platform to introduce various functionalities. The present protocol is particularly attractive because it provides benzocyclobutene analogues in assorted oxidation states by the use of various ketene silyl acetals (Scheme 1).[3] These products can be important synthetic intermediates for various polyaromatic natural products, such as gilvocarcin,[4] pradimicin,[5] aquayamycin,[6] and TAN-1085.[7]

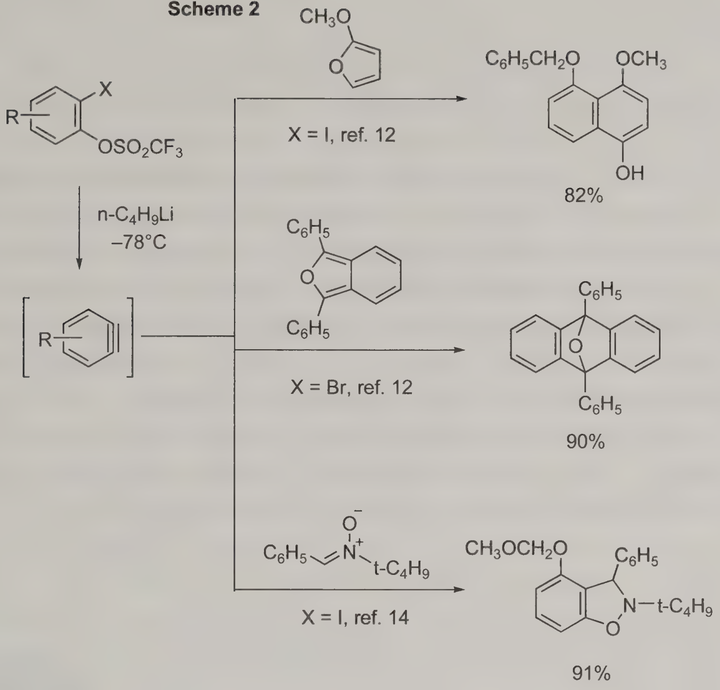
Scheme 1



Arynes are important reactive intermediates, and many studies of their generation and reactions have been undertaken.[8] Several protocols for generation of arynes have been known basically relying on the 1,2-elimination on aromatic rings. These include treatment of aryl halides with a strong base such as sodium amide,[8] decomposition of benzenediazonium-2-carboxylate,[9] halogen–metal exchange on *ortho*-dihalosubstituted benzenes,[10] and treatment of *ortho*-trimethylsilylphenyl triflates with fluoride.[11] However, all methods require high reaction temperatures and/or long reaction times, and often accompanied by side reactions.

In the present procedure, an *ortho*-iodoaryl triflate is employed as an efficient benzyne precursor.[12] This is easily prepared by mono-cleavage of a *bis*-triflate by cesium carbonate[13] and in situ-benzylation of the resulting cesium phenoxide. Benzynes are immediately generated by treatment of the *ortho*-iodoaryl triflate with butyllithium at low temperature (typically –78 ûC). Compared with former methods, the present protocol enables faster generation of benzynes at much lower temperature because of the rapid halogen–lithium exchange and the ability of the triflate to serve as an excellent leaving group. The benzyne intermediate thus generated combines with arynophiles with high-lying HOMOs such as ketene silyl acetals,[3] furans,[12] and nitrones[14] in reactions that afford the corresponding cycloadducts in high yields (Scheme 2).

Scheme 2



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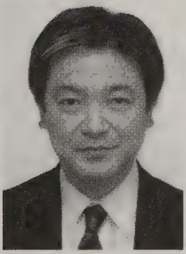
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Resorcinol: 1,3-Benzenediol (9); (108-46-3)
Iodine: HIGHLY TOXIC. CORROSIVE. (9); (7553-56-2)
2-Iodoresorcinol: 1,3-Benzenediol, 2-iodo- (9); (41046-67-7)
N,N-Diisopropylethylamine: Triethylamine, 1,1'-dimethyl- (8); 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)- (9); (7087-68-5)
Trifluoromethanesulfonic anhydride: CORROSIVE: Methanesulfonic acid, trifluoro-, anhydride (9); (358-23-6)
2-Iodoresorcinol bis(trifluoromethanesulfonate): Methanesulfonic acid, trifluoro-, 2-iodo-1,3-phenylene ester (9); (514826-78-9)

Cesium carbonate (7); Carbonic acid, dicesium salt (9); (534-17-8)
3-Hydroxy-2-iodophenyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, 3-hydroxy-2-iodophenyl ester (9); (514826-79-0)
Benzyl bromide: CORROSIVE. LACHRYMATOR: Toluene, α-bromo- (8); Benzene, (bromomethyl)- (9); (100-39-0)
Diethylamine (8); Ethanamine, *N*-ethyl- (9); (109-89-7)
3-Benzyloxy-2-iodophenyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, 2-iodo-3-(phenylmethoxy)phenyl ester (9); (138720-02-2)
1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene: Silane, (1,1-dimethylethyl)[(1-methoxyethenyl)oxy]dimethyl- (9); (77086-38-5)
n-Butyllithium: FLAMMABLE LIQUID: Lithium, butyl- (9); (109-72-8)
Hydrofluoric acid: CORROSIVE. (9); (7664-39-3)
5-Benzyloxybicyclo[4.2.0]octa-1,3,5-trien-7-one: Bicyclo[4.2.0]octa-1,3,5-trien-7-one, 5-(phenylmethoxy)- (9); (169615-68-3)



Keisuke Suzuki was born in 1954. He received his Ph.D. in 1983 from the University of Tokyo under Professor Teruaki Mukaiyama. He began his academic career at Keio University in 1983, and moved to the Tokyo Institute of Technology in 1996. He was the recipient of the Japan Chemical Society Award for Young Chemists in 1986, Japan IBM Award in 1994, Nagoya Silver Medal in 1999, and Synthetic Organic Chemistry Award, Japan in 2003. His research interests include the exploitation of new synthetic methods for selective synthesis of natural products.

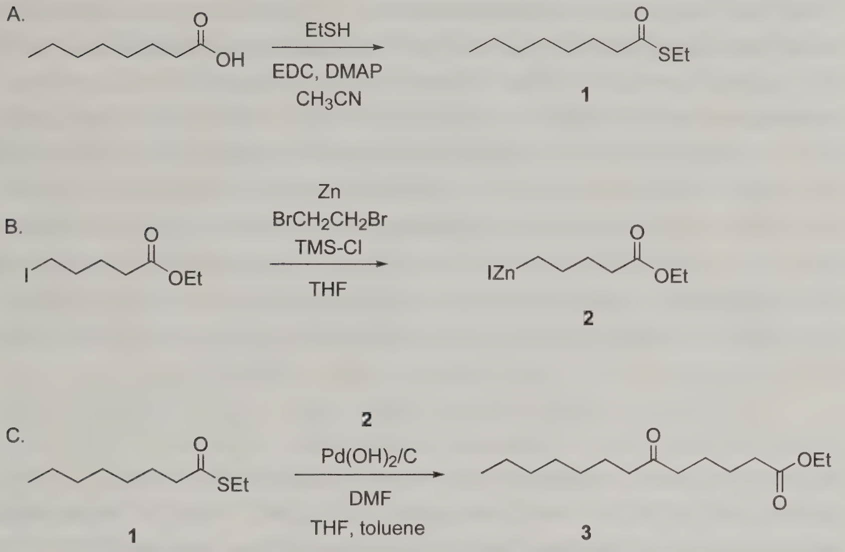
Shin-ichiro Tsujiyama was born in Nagasaki, Japan in 1974. After undergraduate studies at Gifu Pharmaceutical University, he joined the group of Prof. T. Kataoka, and obtained his M.Sc. degree in pharmacology in 1999. Currently he is working for Fujifilm Finechemicals Co., Ltd. in process chemistry, and also is a Ph.D. program student in the group of Prof. K. Suzuki at Tokyo Institute of Technology on studies of benzynes and nitrile oxides.

David B. Guthrie received his B.S. degree at Saint Vincent College of Latrobe, PA in 2003 and performed research with Dr. Daryle Fish. He is currently pursuing his Ph.D. degree at the University of Pittsburgh under the supervision of Prof. Dennis P. Curran. His doctoral studies have included mechanistic investigations of 5-*endo-trig* radical cyclizations, and chiral transfer in reactions of axially chiral *o*-halo anilides.

Heather Gibney was born in 1982 in Pennsylvania, USA. She graduated from Juniata College with a B.S. degree in chemistry where she worked with Professor Richard R. Hark synthesizing tripeptides using solid phase chemistry. She then attended the University of Pittsburgh and in 2006 received her M.S. degree under Professor Dennis P. Curran where she studied radical atom transfer cyclizations. She is now a coatings chemist at Sauereisen, Inc. in Pittsburgh, PA, where she formulates corrosion resistant coatings and technical cements.

SYNTHESIS OF MULTI-FUNCTIONALIZED KETONES THROUGH THE FUKUYAMA COUPLING REACTION CATALYZED BY PEARLMAN'S CATALYST: PREPARATION OF ETHYL 6-OXOTRIDECANOATE

(Tridecanoic acid, 6-oxo-, ethyl ester)



Submitted by Yoshikazu Mori and Masahiko Seki.[1]
Checked by Naohiro Aoyama and Masakatsu Shibasaki

1. Procedure

Caution! All reactions should be conducted in a well-ventilated hood because of the stench of EtSH.

A. S-Ethyl Octanethioate (**1**). A 200-mL, three–necked, round-bottomed flask equipped with a rubber septum, a thermometer, a three-way stopcock connected to an argon balloon (Note 1), and a Teflon-coated magnetic stirring bar is charged with octanoic acid (Note 2) (7.50 g, 52.0 mmol) by a pipette. After being purged with argon in the flask, acetonitrile (CH_3CN) (Note 2) (80 mL) is added by using a measuring cylinder with temporary removal of the septum, while keeping a positive flow of argon. The flask is immersed in an ice-water bath. *N,N*-Dimethylaminopyridine (DMAP) (Note 2) (0.60 g, 4.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (Note 3) (10.0 g, 52.2 mmol) are added successively to the solution while the temperature is kept below 10 °C. The mixture is stirred below 10 °C for 10 min and ethanethiol (EtSH) (Note 2) (3.9 mL, 53 mmol) is added via syringe. The ice-water bath is removed and the mixture is stirred at 25 °C for 22 h (Note 4). The mixture is evaporated (Note 5). The residue is partitioned after adding ethyl acetate (50 mL) and 3.5 % hydrochloric acid (HCl) (50 mL). The organic layer is successively washed with water (50 mL), saturated aqueous sodium hydrogen carbonate (50 mL) and water (50 mL). The organic layer is dried over anhydrous magnesium sulfate ($MgSO_4$) (5.0 g) and filtered. The solid $MgSO_4$ is washed with ethyl acetate (40 mL). The filtrate and the washings are combined and evaporated. The crude material obtained as the residue is purified by column chromatography with a 5-cm diameter column containing 200 g of silica gel (Note 6). The column is eluted with a mixture of hexanes and ethyl acetate (20:1) to give 9.44–9.49 g (50.1–50.4 mmol, 96–97 %) of **1** as a colorless oil (Note 7).

B. 5-Ethoxy-5-oxopentylzinc iodide (**2**). A 100-mL, three–necked, round-bottomed flask is equipped with a reflux condenser (fitted with a three-way stopcock connected to an argon balloon), a thermometer, a rubber septum, and a Teflon-coated magnetic stirring bar. After the apparatus is purged with argon gas, the flask is charged with zinc powder (7.09 g, 108 mmol) (Note 8) with temporary removal of the septum, while keeping a positive flow of argon and anhydrous tetrahydrofuran (THF) (16 mL) (Note 9) via syringe under an argon atmosphere. 1,2-Dibromoethane (240 μL, 2.79 mmol) (Note 10) is added to the stirred suspension via syringe and the mixture is heated to 65 °C and kept at 65 °C for 3 min (Note 11). After cooling the mixture to 25 °C, chlorotrimethylsilane (TMS-Cl; 240 μL, 1.88 mmol) (Note 12) is added via syringe and the slurry is stirred for 15 min at 25 °C (Note 13). The mixture is warmed up to 55–60 °C using an oil bath. Ethyl 5-iodopentanoate (13.8 g, 53.9 mmol) (Note 14) is added to the mixture at 55–60 °C over 90 min via syringe with vigorous stirring (Note 15). The mixture is stirred at 55–60 °C for 30 min and the oil bath is removed. The reaction mixture is allowed to cool to 30–35 °C to give **2** (Note 16). The suspension is used for the subsequent step without further purification.

C. Ethyl 6-Oxotridecanoate (**3**). To the mixture obtained above are added at 30–35 °C, under an argon atmosphere, *S*-ethyl octanethioate (5.04 g, 26.8 mmol) and anhydrous toluene (16 mL) (Note 17) via syringe, Pearlman's catalyst (5% palladium(II) hydroxide on activated carbon) (345 mg, 0.162 mmol) (Note 18) with temporary removal of the septum, while keeping a positive flow of argon and anhydrous *N*,*N*-dimethylformamide (DMF) (2 mL, 25.8 mmol) (Note 17) via syringe. An initial exotherm (from 30–35 °C to approximately 45 °C) is observed. The mixture is stirred at 25 °C for 14 h (Note 19). The reaction mixture is cooled to 5 °C, and 3 M HCl (30 mL) is added to the mixture keeping the temperature below 25 °C (Note 20). The reaction mixture is stirred at 25 °C for 30 min and is filtered. The filtrate is partitioned after addition of ethyl acetate (120 mL). The organic layer is washed with water (60 mL x 2) and dried over anhydrous $MgSO_4$ (6 g). The mixture is filtered and the $MgSO_4$ is washed with ethyl acetate (45 mL). The filtrate and the washings are combined and evaporated to afford 10.2 g of yellow oil (Note 21). The crude material is purified by chromatography on a 5-cm diameter column containing 200 g of silica gel (Note 6). The column is eluted with a mixture of hexanse and ethyl acetate (15:1) to give 5.35 g (20.9 mmol, 78 %) of **3** as a pale yellow oil (Note 22).

2. Notes

1. The submitters performed the reaction under a nitrogen atmosphere.

2. Octanoic acid, acetonitrile, DMAP, and EtSH were purchased from Aldrich Chemical Company, Inc., and used as received.

3. EDC was purchased from Tanabe Seiyaku Co., Ltd., Fine Chemicals Division and used as received.

4. The conversion of the reaction was monitored by TLC (hexanes/ethyl acetate = 8:1, phosphomolybdic acid was used as stain, silica gel was used as stationary phase, octanoic acid: $R_f = 0.2$, product (*S*-ethyl octanethioate): $R_f = 0.85$.

5. Checkers conducted the evaporation at 50 °C under approximately 30 mmHg. In order to control the odor, the vapor output from evaporator was passed through a trap cooled at –78 °C by dry ice-acetone bath.

6. Silica gel 60, particle size 230–400 mesh ASTM, Merck Ltd. was used.

7. The physical properties of the product were as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 3 H, J = 7.1 Hz). 1.34–1.21 (m, 11 H), 1.69–1.62 (m, 2 H), 2.55–2.51 (m, 2 H), 2.87 (q, 2 H, J = 7.4 Hz); ^{13}C NMR

(125 MHz, $CDCl_3$) δ: 14.0, 14.8, 22.6, 23.2, 25.7, 28.9, 28.9, 31.6, 44.1, 199.8; IR (neat): 2928, 2857, 1692 cm^{-1}; MS (ESI) *m/z* 211 $[M + Na]^+$. HRMS (EI) *m/z* $[M–SEt]^+$: Calcd for $C_8H_{15}O$, 127.1117; Found, 127.1119. Anal. Calcd for $C_{10}H_{20}OS$: C, 63.77; H, 10.70. Found: C, 63.52; H, 10.44.

8. Zinc powder was purchased from Merck (GR for analysis, particle size <45 μm, Merck 108789), and used as received.

9. The submitters used anhydrous THF distilled from lithium aluminum hydride and stored over molecular sieves 4Å. The checkers used anhydrous THF freshly distilled from sodium/benzophenone ketyl under argon prior to use.

10. 1,2-Dibromoethane was purchased from Aldrich Chemical Company, Inc. (submitters) or Tokyo Kasei Kogyo Co., Ltd. (checkers) and used as received.

11. The checkers kept the internal temperature at 65 °C for 3 min after the internal temperature reached 65 °C (oil bath temperature was approximately 75 °C).

12. TMS-Cl was purchased from Aldrich Chemical Company, Inc., and used as received.

13. Checkers observed evolution of gas after addition of TMS-Cl.

14. Ethyl 5-iodopentanoate was purchased from Tanabe Seiyaku Co., Ltd., Fine Chemicals Division and was freshly distilled before use (bp 91–95 °C/7 mmHg).

15. The addition period depended on the scale of the reaction. An extended addition time of up to 2 h did not affect the reaction. Consistent addition of the iodide with control of the internal temperature at the indicated range (55–60 °C) was critical to ensure the completion of the reaction. The checkers kept the inner temperature at 60 °C.

16. The conversion of the reaction was assessed by the following procedures: (A, submitters' procedure) an aliquot of the reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate and subjected to the HPLC analysis (Inertsil ODS-2, 40 °C, 50 mM KH_2PO_4 (pH 3.0)/MeOH = 30:70, 0.8 mL/min, 210 nm, ethyl pentanoate: 5.4 min, ethyl 5-iodopentanoate: 6.4 min, the intensity of ethyl 5-iodopentanoate is 1.9 times higher than that of ethyl pentanoate). (B, checkers' procedure) an aliquot of the reaction mixture was quenched with 1 M HCl and extracted with $CDCl_3$ (chloroform-d) and subjected to the ^1H NMR (500 MHz, $CDCl_3$) analysis (ethyl pentanoate: δ: 0.92 ($\underline{CH_3}(CH_2)_3CO_2Et$, t, J = 7.3 Hz), ethyl 5-iodopentanoate: δ: 3.19 ($I\underline{CH_2}(CH_2)_3CO_2Et$, t, J = 7.1 Hz)). Integration of these signals showed less than 1% of ethyl 5-iodopentanoate and more

than 99% of ethyl pentanoate was detected.

17. Toluene and DMF were purchased from Aldrich Chemical Company, Inc., and dried over molecular sieves 4Å before use.

18. Pearlman's catalyst (Degussa nomenclature, E101NE/D) was purchased from Degussa Japan Co., Ltd. Pearlman's catalyst was added as a solid under argon flow.

19. The checkers immersed the reaction flask in the oil bath to keep the outer temperature at 25 °C. The conversion of the reaction was monitored by TLC (hexanes/ethyl acetate = 8 : 1, phosphomolybdic acid was used as an indicator, SM (*S*-ethyl octanethioate): $R_f = 0.85$, product (ethyl 6-oxotridecanoate): $R_f = 0.4$).

20. The reaction mixture produced an unpleasant odor due to the formation of EtSH.

21. The checkers conducted the evaporation at 50 °C under 36 mmHg. The submitters reported that the crude material weighed 8.1 g.

22. The physical properties of the product were as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.20–1.34 (m, 11 H), 1.52–1.65 (m, 6 H), 2.31 (t, 2 H, *J* = 7.1 Hz), 2.36–2.44 (m, 4 H), 4.12 (q, 2 H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 14.2, 22.6, 23.2, 23.9, 24.5, 29.1, 29.2, 31.7, 34.1, 42.3, 42.9, 60.3, 173.4, 211.0. IR (neat): 2929, 2857, 1736, 1179 cm^{-1}. HRMS (FAB) *m/z* $[M+H]^+$: Calcd for $C_{15}H_{29}O_3$, 257.2111; Found, 257.2110. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 69.99; H, 10.86.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Palladium-catalyzed coupling reactions have found wide application in the preparation of valuable compounds such as drugs and natural products. One of the most attractive features of palladium-catalyzed coupling reactions is its wide applicability to the substrates carrying various functional groups. Tedious protection-deprotection sequences, as well as functional group transformations are often avoided. Fukuyama and co-workers have recently developed a highly efficient synthetic method for the generation of ketones.[2] Treatment of thiol esters with zinc reagents in the presence of dichlorobis(triphenylphosphine) palladium(II) [$PdCl_2(PPh_3)_2$] provides highly functionalized ketones in excellent yields. The reaction is featured by unusually high chemoselectivity, mild reaction conditions and the use of less-toxic reagents. However, requirement of the expensive palladium catalyst has hindered the commercial application of the technology.

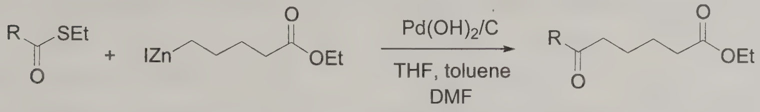
The use of heterogeneous palladium catalysts to perform the coupling chemistry described above enables facile recovery of palladium, as well as eliminates metal contamination of the product. The heterogeneous catalytic process thus provides a reaction that is much more cost conscious, compared with the homogeneous counterparts. The present procedure employs heterogeneous Pearlman's catalyst (palladium(II) hydroxide on activated carbon, $Pd(OH)_2/C$).[3] Use of this catalyst is advantageous in terms of low catalyst loading and safe handling of the catalyst, which is less flammable.

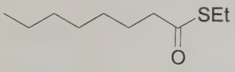
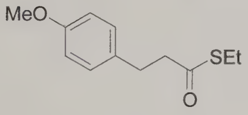
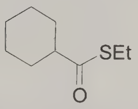
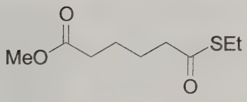
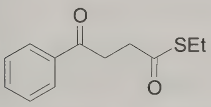
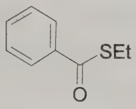
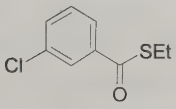
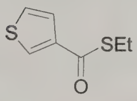
The method was tested in the reaction of various functionalized thiol esters with the zinc reagent (Table 1). The reaction between the zinc reagent and primary or secondary alkyl thiol esters with or without an ester or a keto group afforded the corresponding ketones in good yields (Table 1, Entries 2-5). The reaction using an aromatic thiol ester carrying a chloro or a sulfide group provided a good yield, as well (Table 1, Entries 7, 8).

In the workup as originally performed, the reaction mixture was filtered directly through Celite to recover the palladium catalyst. However, viscous zinc salts in the reaction mixture often required a prolonged period for filtration. As an improvement, prior to filtration, aqueous hydrochloric acid was added to the reaction mixture. The aqueous hydrochloric acid dissolved the zinc salts and permitted separation of the zinc-free Pd catalyst as a filter cake. No palladium was detected in the filtrate and recovery of palladium from the filter cake was more than 95%.

The present procedure was applied to the introduction of the side chain of (+)-biotin[4] (Scheme 1).[5] The zinc reagent was allowed to react with thiolactone {(*4S,5R*)-1,3-dibenzyl-3,3a,6,6a-tetrahydro-1*H*-thieno[3,4-*d*]-imidazol-2,4-dione} to afford, after dehydration with hydrochloric acid, a compound carrying the required side chain in high yield. The product is readily converted to (+)-biotin by hydrogenation and subsequent removal of protective groups.[6] Through the present process, (+)-biotin is obtained in three steps from thiolactone, which is three steps shorter than the conventional method that employs a Grignard reaction.[7] The reduced number of steps, high yield, operational simplicity, ready availability of the reagents and mild reaction conditions of the process provides a much more practical route to (+)-biotin.

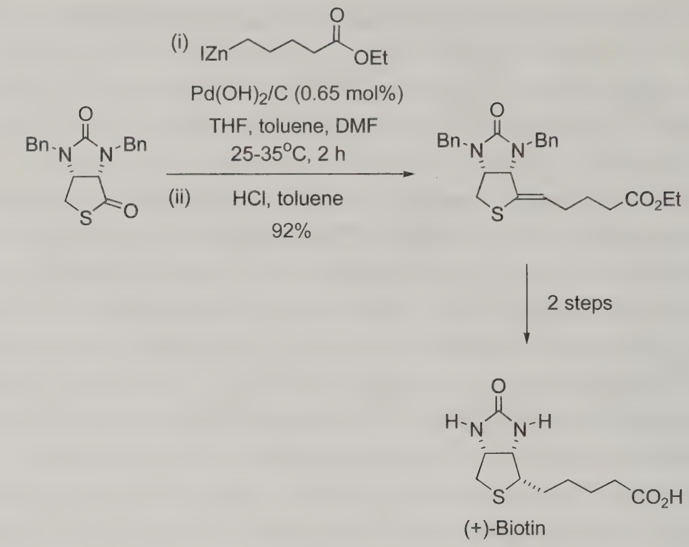
Table 1. Fukuyama coupling reaction in the presence of $Pd(OH)_2/C$.



Entry	Thiol Ester	Catalyst Loading (mol % Pd)	Reaction Time (h)	Yield (%)[a]
1		0.6	14	78
2		0.15	50	84
3		0.6	72	79
4		0.9	17	78
5		0.9	23	70
6		0.9	71	72
7		0.6	25	73
8		0.9	68	61

[a]Isolated Yield.

Scheme 1



1. Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-Ku, Osaka 532-8505, Japan.
2. (a) Tokuyama; H.; Yokoshima; S.; Yamashita; T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189; (b) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477; (c) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett* **2003**, 1512; (d) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.
3. Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571.
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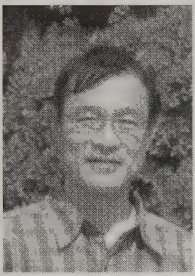
7. (a) Goldberg, M. W.; Sternbach, L. H. US Pat 2489232, **1949**; *Chem. Abst.* **1951**, *45*, 184. (b) Goldberg, M. W.; Sternbach, L. H. US Pat 2489235, **1949**; *Chem. Abst.* **1951**, *45*, 186s. (c) Goldberg, M. W.; Sternbach, L. H. US Pat 2489238, **1949**; *Chem. Abst.* **1951**, *45*, 186g. (d) Gerecke, M.; Zimmermann, J.-P.; Ashwanden, W. *Hel. Chim. Acta* **1970**, *53*, 991.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Octanoic acid; (124-07-2)
N,N-Dimethylaminopyridine: 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3)
1,3-Propanediamine, *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-,
monohydrochloride ; (25952-53-8)
Ethanethiol: STENCH; (75-08-1)
1,2-Dibromoethane: CANCER SUSPECT AGENT; (106-93-4)
Chlorotrimethylsilane; (75-77-4)
Ethyl 5-iodopentanoate: CANCER SUSPECT AGENT: Pentanoic acid,
5-iodo-, ethyl ester; (41302-32-3)
Palladium hydroxide; (12135-22-7)
Ethyl pentanoate: Pentanoic acid, ethyl ester; (539-82-2)

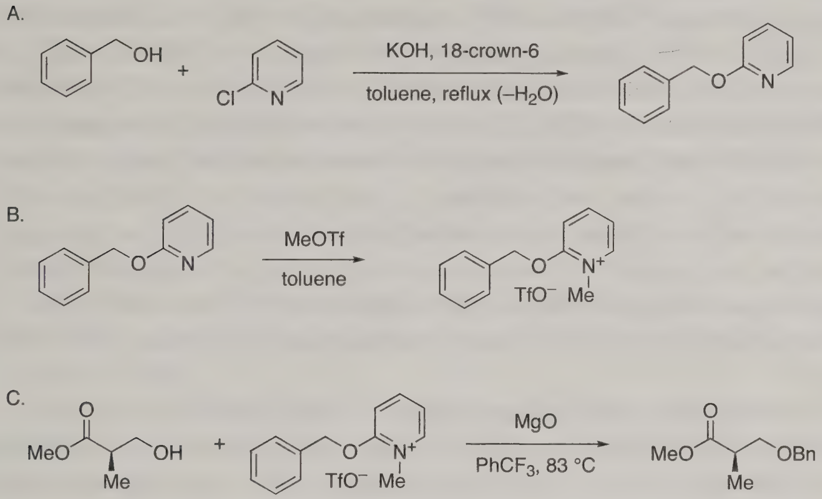


Masahiko Seki was born in 1957 in Kyoto, Japan. He obtained his M.S. degree in 1982 from Kyoto University under the supervision of professor Yuzo Inouye and, in the same year, joined Tanabe Seiyaku Co., Ltd., where he became a senior scientist in 1999. He received his Ph.D. degree from Kyoto University in 1988. From 1993, he spent a year as a postdoctoral fellow at Colorado State University under the direction of professor Albert I. Meyers. His research interests focus on the development of efficient and practical synthesis of biologically active compounds by means of novel synthetic methodologies.

Yoshikazu Mori was born in Kurashiki, Japan in 1963. He received a Master's degree in Engineering from Graduate School of Engineering, Kyoto University. He joined Tanabe Seiyaku Co, Ltd. in 1991. He is engaged in research and development of efficient and practical pharmaceutical process.

Naohiro Aoyama was born in 1979 in Fukui, Japan, and received his Ph.D. from the University of Tokyo in 2006 under the direction of Professor Shu Kobayashi. Then he joined Professor Masakatsu Shibasaki's group as a postdoctoral fellow. He joined the medicinal chemistry department at Astellas Pharma Inc. in April 2007.

PROTECTION OF ALCOHOLS USING 2-BENZYLOXY-1-METHYLPYRIDINIUM TRIFLUOROMETHANESULFONATE: METHYL (R)-(–)-3-BENZYLOXY-2-METHYL PROPANOATE



Submitted by Kevin W. C. Poon, Philip A. Albiniak, and Gregory B. Dudley.[1]
Checked by Martin A. Berliner and John A. Ragan.[2]

1. Procedure

Caution: *Exercise care in the handling of 18-Crown-6 (harmful, target organ: nerves) and methyl triflate (corrosive, causes burns, target organs: eyes, skin, mucous membranes).*

A. 2-Benzyloxypyridine. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, a thermocouple probe, a glass stopper, and a Dean-Stark trap with reflux condenser and a nitrogen bubbler (Note 1) is charged with benzyl alcohol (11.7 g, 0.108 mol, 1.0 equiv), 2-chloropyridine (13.5 g, 0.119 mol, 1.1 equiv) (Note 2), potassium hydroxide (20.0 g, 0.356 mol, 3.3 equiv) (Note 3), and toluene (210 mL) (Note 4) by temporary removal of the glass stopper. The suspension is stirred and 18-crown-6 (1.43 g, 5.40 mmol, 0.05 equiv) (Note 2) is added in one portion. The reaction mixture is heated to reflux (Note 5) with azeotropic removal of water (Note 6) for 1 h. The reaction mixture is then allowed to cool to 25 °C. The fittings of the flask are removed. Water (100 mL) is added to the cooled reaction mixture and the resulting biphasic solution is transferred to a 500-mL separatory funnel. The reaction flask is rinsed with 50 mL of toluene and the rinse is combined with the reaction mixture. The lower, strongly basic aqueous layer (pH 14) is removed. The organic phase is washed a second time with water (100 mL) and the aqueous layer (pH ~7) is removed. The cloudy, colorless organic phase is transferred to a 500-mL flask and concentrated under reduced pressure on a rotary evaporator (25–45 mmHg, bath temperature 45–50 °C). Residual water remaining in the organic phase is azeotropically removed during the concentration, to provide the crude product as a clear and colorless to pale yellow oil. This material is transferred to a 100-mL single-necked round-bottomed flask with magnetic stir bar and purified by vacuum distillation using a short-path distillation apparatus. A single fraction is collected (bp 93–95 °C, 1.0 mmHg) providing 19.0–19.2 g (95–96%) of 2-benzyloxypyridine as a colorless liquid (Notes 7,8).

B. 2-Benzyloxy-1-methylpyridinium trifluoromethanesulfonate. A three-necked, 250-mL, round-bottomed flask equipped with a nitrogen bubbler inlet (Note 1), thermocouple probe, rubber septum and overhead mechanical stirrer (Note 9) is charged with 2-benzyloxypyridine (10.6 g, 57.3 mmol, 1.0 equiv) and toluene (60 mL) (Note 4) by temporary removal of the septum. The resulting solution is cooled to 0 °C in an ice bath. Methyl trifluoromethanesulfonate (6.80 mL, 60.1 mmol, 1.05 equiv) (Note 10) is added dropwise via syringe over 15 min, during which time white solids crystallize and the internal temperature increases to approximately 15 °C. The ice bath is removed and the viscous slurry is allowed to warm to ambient temperature. After 1 h (Note 11), the heterogeneous reaction mixture is diluted with 50 mL of hexanes (Note 12) and the solids are isolated by filtration and washed with one additional portion of hexanes (50 mL). After drying under vacuum, 19.6–19.8 g (98.5–99%) of 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate is isolated as a white, microcrystalline solid (Note 13).

C. Methyl (R)-(–)-3-benzyloxy-2-methyl propanoate. An oven-dried, 250-mL, three-necked, round-bottomed flask is equipped with a reflux condenser with an inert gas bubbler, a magnetic stir bar, a thermocouple probe and a glass stopper. 2-Benzyloxy-1-methylpyridinium trifluoromethanesulfonate (16.7 g, 48.0 mmol, 2.0 equiv) (Note 14), magnesium oxide (1.94 g, 48.0 mmol, 2.0 equiv) (Note 15), α,α,α-trifluorotoluene (48 mL) (Note 16) and methyl (*R*)-(–)-3-hydroxy-2-methyl propionate (2.65 mL, 23.8 mmol, 1.0 equiv) (Note 17) are charged to the reaction flask by temporarily removing the glass stopper. The heterogeneous reaction mixture is then heated in an oil bath (83 °C bath temperature, 80–82 °C internal temperature) for 24 h (Note 18). The reaction mixture is allowed to cool to room temperature and suction filtered through a pad of Celite on a sintered glass funnel. The Celite is washed with methylene chloride (2 x 20 mL). The filtrate is concentrated by rotary evaporation (15 mmHg, 25 °C bath temperature), and the light brown oil is purified by flash column chromatography (Note 19) to provide 3.77–4.10 g (76–82%) of methyl (*R*)-(–)-3-benzyloxy-2-methyl propanoate as a colorless liquid (Notes 20, 21).

2. Notes

1. The submitters conducted this procedure under an atmosphere of argon; the checkers found substitution of nitrogen to have no adverse impact on yield or purity.

2. Benzyl alcohol (99%), 2-chloropyridine (99%), and 18-crown-6 (99%) were purchased from Sigma-Aldrich and used without further purification.

3. Potassium hydroxide pellets were purchased from J. T. Baker and ground with a mortar and pestle immediately before use.

4. The submitters purchased toluene from VWR and passed it through neutral alumina and 4Å molecular sieves columns under argon atmosphere before use. The checkers obtained ACS grade toluene from Sigma-Aldrich and used it as received.

5. The checkers utilized a heating mantle and a solid state heating controller set to 125 °C at approximately 80% power to maintain reflux. The submitters utilized an oil bath (150 °C bath temperature).

6. At the end of the reaction, 1.4 mL of water was collected in the Dean-Stark trap.

7. The checkers performed a simple distillation under vacuum with the distillation pot heated in an oil bath set at 120 °C. The submitters employed fractional vacuum distillation using a short-path distillation apparatus fitted with a 3-neck pig adapter and thermometer and connected to a vacuum oil pump (0.25 mmHg).

8. The compound had the following physical data: bp: 93–95 °C/ 1.0 mmHg. IR (thin film): 1594, 1569, 1472, 1430, 1270, 988, 777, 733, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.36 (s, 2 H), 6.80 (dt, *J* = 8.4, 0.9 Hz, 1 H), 6.87 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1 H), 7.30 (m, 1 H), 7.34–7.39 (m, 2 H), 7.44–7.49 (m, 2 H), 7.57 (ddd, *J* = 8.4, 7.1, 2.0 Hz, 1 H), 8.17 (ddd, *J* =

5.1, 2.0, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.5, 111.3, 116.9, 127.8, 127.9, 128.4, 137.3, 138.6, 146.8, 163.6; Anal: Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.56; H, 6.07; N, 7.32. R_f = 0.64 (250 μm silica gel on glass, hexanes:ethyl acetate = 3:1, UV visualization). The spectral data for 2-benzyloxypyridine matched that of the literature data.[3]

9. The submitters used magnetic stirring for this reaction. The checkers observed that cooling of the thick slurry was much less efficient with magnetic stirring than with mechanical stirring at the scale of this preparation.

10. Methyl trifluoromethanesulfonate (MeOTf) was purchased from Sigma-Aldrich, stored and handled under an atmosphere of argon, and used without further purification.

11. TLC analysis showed disappearance of 2-benzyloxypyridine within 1 h by TLC (R_f (reaction product) = 0; R_f (starting material) = 0.6; 3:1 hexanes:EtOAc; UV visualization) and by HPLC (product t_R 2.7 min; starting material t_R 2.4 min; Agilent Zorbax SB-CN column, 4.2 × 75 mm, 3.5 μ silica; mobile phases 0.1% $HClO_4/H_2O$ and acetonitrile; isocratic 95:5 aqueous:acetonitrile for 0.25 min, ramp to 10:90 over 5 min; isocratic at 10:90 for 0.75 min, flow 2 mL/min, UV detection at 210 nm, 30 °C column temperature).

12. The checkers obtained ACS grade hexanes from Sigma-Aldrich and used it as received.

13. Further purification of the material thus obtained was not necessary. The compound had the following physical data: mp: 92–93 °C. IR (thin film): 1639, 1587, 1518, 1254, 1148, 1028, 772, 751, 699, 633 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.07 (s, 3 H), 5.54 (s, 2 H), 7.38–7.52 (m, 6 H), 7.60 (d, J = 8.8 Hz, 1 H), 8.31 (ddd, J = 1.8, 7.5, 9.2 Hz, 1 H), 8.47 (dd, J = 6.4, 1.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.8, 74.3, 112.0, 119.0, 120.6 (q, J_{CF} = 320 Hz), 128.5, 128.9, 129.5, 132.5, 143.7, 148.0, 159.4; ^{19}F NMR (376 MHz, $CDCl_3$, external reference to TFA) δ: –78.8 (s); MS (APCI+) 200.2 $(M–OTf)^+$. Anal: Calcd for $C_{14}H_{14}F_3NO_4S$: C, 48.14; H, 4.04; N, 4.01; Found: C, 48.27; H, 3.73; N, 3.95. The submitters also reported the following data: HRMS (ESI+) found 200.1070 $(M-OTf)^+$ (calcd for $C_{13}H_{14}NO^+$: 200.1075) CHFNOS analysis: Calcd for $C_{14}H_{14}F_3NO_4S$: C, 48.14%; H, 4.04%; F, 16.31%; N, 4.01%; O, 18.32%; S, 9.18%. Found: C, 48.24%; H, 4.09%; F, 16.27%; N, 4.10%; O, 18.53%; S, 9.31%.

14. A minimum of 1.8 equiv of 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate was found to be necessary for complete

consumption of the alcohol substrates. Dibenzyl ether (Bn_2O) was formed as a by-product during the course of the reaction, perhaps through reaction of the pyridinium salt with MgO and/or adventitious moisture to generate benzyl alcohol *in situ*.

15. The checkers obtained magnesium oxide (light) from Sigma-Aldrich and dried it in a vacuum oven at 60 °C for 12 h. The submitters dried magnesium oxide under vacuum in a flask immersed in an oil bath for 6 h and stored under an atmosphere of argon.

16. α,α,α-Trifluorotoluene in a Sure/Seal bottle was purchased from Sigma-Aldrich and used without further purification.

17. Methyl (*R*)-(–)-3-hydroxy-2-methyl propanoate (99% ee) was purchased from Sigma-Aldrich and used without further purification.

18. The reaction mixture was analyzed by thin layer chromatography (TLC, 250 μm silica gel on glass, hexanes/ethyl acetate = 9:1); visualization was accomplished with 254 nm UV light and anisaldehyde stain with heating: R_f (starting alcohol) = 0.08; R_f (benzyl ether product) = 0.36; R_f (dibenzyl ether by-product) = 0.61.

19. The checkers utilized 120 g of silica gel (60Å, 230–400 mesh) loading the sample neat and used a gradient (19:1 heptanes:EtOAc to elute Bn_2O, to 9:1 heptanes:EtOAc to elute the desired product). The submitters utilized a silica gel column (16 cm length × 4.5 cm width, 90 g of Silica Gel 60 Geduran® 40-63 μM) wet-loaded as a slurry, loading the sample in a minimum volume of eluent, and eluting the product with 750 mL 19:1 hexanes:EtOAc.

20. Careful analysis of the ^1H NMR spectrum prior to chromatography and LC/MS analysis of the purified product indicated that impurities were formed from bis- and tris-benzylation (i.e. M+Bn and M+2Bn), presumably by addition to the aromatic ring of the primary benzyl ether product. These impurities seemed to have a greater response factor than the desired product, as their apparent level by LC/MS analysis was significantly higher than that indicated by ^1H NMR or elemental analysis. For example, the elemental analysis in Note 21 corresponded to less than 5% of the bis-benzyl product ($C_{19}H_{22}O_3$, vs. $C_{12}H_{16}O_3$ for the desired), and the ^1H NMR spectrum showed no discernable quantities of any impurity. This level of impurity should not be an issue for the vast majority of applications of this methodology, but the readers should be aware of the potential presence of these side products.

21. The compound had the following physical data, which matched the data in the literature.[4] ^1H NMR (400 MHz, $CDCl_3$) δ:1.16 (d, J = 7.1 Hz,

3 H), 2.79 (X of $ABXY_3$, ddq, J_{BX} = 5.9 Hz, J_{AX} = 7.4 Hz, J_{XY} = 7.1 Hz, 1 H), 3.47 (B of $ABXY_3$, dd, J_{AB} = 9.1 Hz, J_{BX} = 5.9 Hz, 1 H), 3.64 (A of $ABXY_3$, dd, J_{AB} = 9.1 Hz, J_{AX} = 7.4 Hz, 1 H), 3.68 (s, 2H), 4.50 (B of AB, J = 12.4 Hz, 1 H), 4.51 (A of AB, J = 12.4 Hz, 1 H), 7.26–7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:13.9, 40.1, 51.7, 71.9, 73.0, 127.51, 127.53, 128.3, 138.1, 175.2; IR (thin film, cm^{-1}): 1736, 1454, 1363, 1198, 1176, 1092, 1028, 736, 698, 608. Anal: Calc'd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.57; H, 7.86. $[\alpha]_D$ –10.4° (c 2.8, $CHCl_3$); lit $[\alpha]_D$ –10.6° (c 1.7, $CHCl_3$).[5] R_f = 0.36 (250 μm silica gel on glass, hexanes/ethyl acetate = 9:1). Chiral HLPC analysis (Chiracal OD-H 0.46 × 25 cm, 98:2 heptane:2-propanol mobile phase at 1.5 mL/min flow) indicated >99% ee. The (*R*) enantiomer eluted at 3.88 min; the (*S*) enantiomer eluted at 4.17 min.

Waste Disposal Information

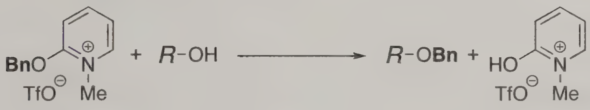
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Benzyl ethers are important protecting groups in organic synthesis due to their stability and the minimal electronic impact that they impart on the oxygen atom to which they are attached.[6] For example, benzyl ethers do not interfere with chelation-controlled addition of external nucleophiles to chiral aldehydes, in contrast to silyl ethers.[7] Benzyl (and modified arylmethyl) ethers are perhaps the most versatile of the alkyl ethers with respect to modes of cleavage, which include hydrogenolysis, oxidation, dissolving metal reduction, and acidic decomposition under a range of experimental protocols.

Standard conditions for the formation of benzyl ethers from the corresponding alcohols fall into two main categories: (1) the Williamson ether synthesis, an S_N2-type reaction between benzyl bromide and alkali metal alkoxides, and (2) coupling using benzyl trichloroacetimidate, which is generally promoted by trifluoromethanesulfonic acid (triflic acid, TfOH).[8] Typical benzylation reactions are thus limited to substrates that tolerate either strongly acidic or basic conditions.

2-Benzyloxy-1-methyl-pyridinium trifluoromethanesulfonate (**1**) provides benzyl ethers upon warming in the presence of a free alcohol.[9] The overall balanced equation for the benzylation of alcohols (**2** → **3**) is shown in Eq 1. In contrast to activated acetimidates, oxypyridinium salt **1** is stable to storage and handling. At room temperature, **1** is soluble in chlorinated solvents (dichloromethane, chloroform, dichloroethane), partially soluble in ethereal solvents (THF and ether), and insoluble in aromatic hydrocarbons (benzene, toluene). However, mixtures of **1** and aromatic solvents become homogeneous at elevated temperatures.



(1)

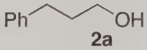
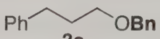
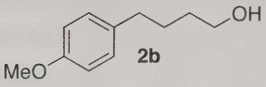
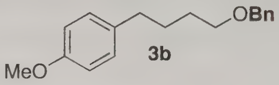
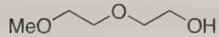
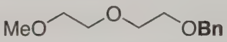
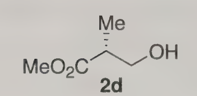
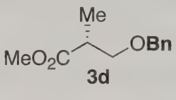
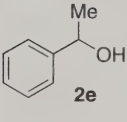
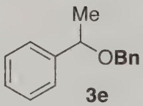
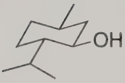
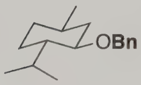
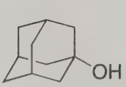
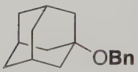
1 **2** **3** **4**

Table 1 illustrates the benzylation reactions of representative alcohols. Primary (entries 1-4) and secondary (entries 5-6) alcohols and certain tertiary alcohols (entry 7) provided the desired benzyl ethers (**3a-g**) in good to excellent yield. Note that phenols are not included in Table 1; aromatic alcohols have yet to be demonstrated as viable substrates in this reaction. However, Mitsunobu conditions[10] can be applied to the benzylation of most phenols.

In conclusion, 2-benzyloxy-1-methylpyridinium triflate (**1**) is a novel benzylation reagent for alcohols. Salt **1** is easy to prepare, bench-stable, and pre-activated. No acidic or basic promoters are needed for benzyl transfer, which occurs upon warming in the presence of the alcohol substrate under mild conditions. New arylmethylation reagents should find use in organic synthesis for the protection of sensitive alcohol substrates.

Table 1. Scope of the Benzylation Reaction

$$\begin{array}{c} \text{1.0 equiv } R\text{–OH } (\mathbf{2}) \\ + \\ \text{2.0 equiv } \mathbf{1} \end{array} \xrightarrow[\text{PhCF}_3\text{, 83 °C, 1 d}]{\text{2.0 equiv MgO}} \begin{array}{c} R\text{-OBn} \\ \mathbf{3} \end{array}$$

Entry	ROH (2)	ROBn (3)	Yield[a]
1.	 **2a**	 **3a**	>95%
2.	 **2b**	 **3b**	>95%
3.	 **2c**	 **3c**	>95% 93%[b]
4.	 **2d**	 **3d**	85% 76–82%[b]
5.	 **2e**	 **3e**	83%
6.	 **2f**	 **3f**	88%
7.	 **2g**	 **3g**	80%

[a] Yields are estimated by ^{1}H NMR spectroscopy, unless otherwise indicated.
[b] Isolated yield of pure product.

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2. Chemical Research and Development, Pfizer Global Research and Development, Groton, CT, 06340.
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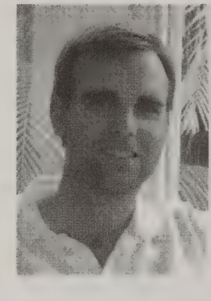
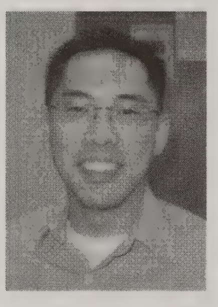
10. Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Benzyl alcohol: Benzenemethanol; (100-51-6)
2-Chloropyridine; (109-09-1)
2-Benzyloxypyridine: Pyridine, 2-(phenylmethoxy)-; (40864-08-2)
2-Benzyloxy-1-methylpyridinium trifluoromethanesulfonate; (882980-43-0)
Methyl trifluoromethanesulfonate: Methyl trifluoromethanesulfonate; (333-27-7)
Methyl (*R*)-(–)-3-benzyloxy-2-methyl propanoate: Propanoic acid, 2-methyl-3-(phenylmethoxy)-, methyl ester, (2*R*)-; (112068-34-5)
Magnesium oxide; (1309-48-4)
Methyl (*R*)-(–)-3-hydroxy-2-methyl propionate; Propanoic acid, 3-hydroxy-2-methyl-, methyl ester, (2*R*)-; (72657-23-9)



Gregory B. Dudley was born in 1974 in Chicago and raised in Miami, FL. Despite a vow never to take chemistry again after high school, GBD got a PhD in the subject at MIT from Rick Danheiser and was an NIH Postdoctoral Fellow with Sam Danishefsky. In 2002, Dudley returned to his alma mater, FSU, as an assistant professor. Professor Dudley (who still goes by "Greg" amongst his closest family) enjoys Costa Rican coffee, armchair philosophy, and synthetic organic chemistry.



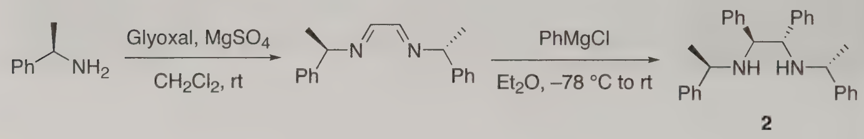
Kevin Wing C. Poon received his B.S. degree in 1996 and M.S. degree in 1998. He then continued his graduate studies with Professor Paul R. Hanson at the University of Kansas and received his Ph.D. degree in Chemistry in 2004. After graduation he moved to the Florida State University for his postdoctoral studies with Professor Gregory B. Dudley. Currently, he is a postdoctoral researcher in the medicinal chemistry department at the University of Kansas where his research focuses on combinatorial chemistry.

Philip A. Albiniak was born in Myrtle Beach, SC and received B.S. degrees in chemistry and biochemistry from the College of Charleston in 2000. Later that fall, he moved to Princeton University to begin graduate studies in chemistry under the direction of Martin F. Semmelhack. In the fall of 2006 he moved to Florida State University to begin a postdoctoral association with Greg Dudley. His current research focuses on the synthetic applications of oxypyridinium salts as well as the total synthesis of roseophilin.

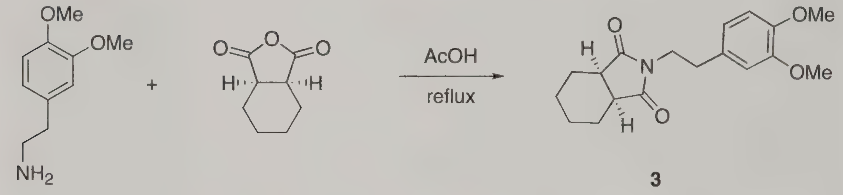
Marty Berliner was born in Denver, Colorado in 1968. He received a B.S. in Physics from Harvey Mudd College in 1990 and then switched fields to organic chemistry in graduate school, where he earned a Ph.D. with Tarek Sammakia (University of Colorado, Boulder) developing the asymmetric Diels-Alder reaction of oxocarbenium ions (1996). Following postdoctoral research with David Williams at Indiana University, he joined Pfizer in 1999 and is currently a senior principal scientist in the early candidate group in Chemical Research and Development.

CHIRAL LITHIUM AMIDE BASE DESYMMETRIZATION OF A RING FUSED IMIDE: FORMATION OF (3a*S*,7a*S*)-2-[2-(3,4-DIMETHOXYPHENYL)-ETHYL]-1,3-DIOXO-OCTAHYDRO-ISOINDOLE-3a-CARBOXYLIC ACID METHYL ESTER

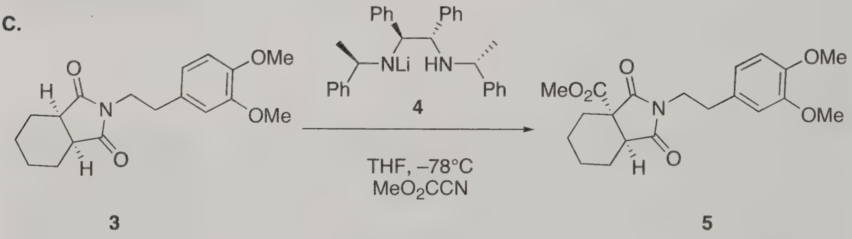
A.



B.



C.



Submitted by Vincent Rodeschini, Nigel S. Simpkins and Fengzhi Zhang.[1]
Checked by Melissa A. Beenen and Jonathan A. Ellman.

1. Procedure

A. 1(S),2(S)-Diphenyl-N,N'-bis-[1(R)-phenyl-ethyl]-ethane-1,2-diamine (2). In a 500-mL, three-necked, round-bottomed flask equipped with a N_2 inlet, two septa and a magnetic stirring bar is introduced successively CH_2Cl_2 (180 mL) (Note 1) and an aqueous glyoxal solution (9.40 mL, 82.5 mmol, 1.0 equiv) (Note 2) by syringe through one of the septa. One septum is temporarily removed and solid magnesium sulfate (40.0 g) (Note 3) is then added portion-wise over 20 min, while the mixture is stirred at room temperature. The resulting suspension is stirred for an

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additional 10 min, and then (*R*)-(+)-phenylethylamine (21.0 mL, 20.0 g, 165.0 mmol, 2.0 equiv) (Note 4) is introduced dropwise *via* syringe over a 5 min period. The resulting mixture is stirred overnight at room temperature. Magnesium sulfate is removed by filtration and rinsed with CH_2Cl_2 (2 × 25 mL). The filtrate is then concentrated by rotary evaporation and then further dried under high vacuum for 1 h (Note 5) to provide crude bis-imine (**1**) (Note 6) as an orange oil (21.3 g, 98.0%), which is used directly for the next step without further purification. Into a 1-L, three-necked, round-bottomed flask (Note 7) equipped with one low temperature thermometer, one N_2 inlet and one septum is introduced crude bis-imine **1** (21.3 g) as a solution in Et_2O (300 mL) by syringe (Note 8). This solution is cooled to –78 °C (dry ice-acetone bath), and PhMgCl (162 mL, 2.0 M in THF, 325 mmol, 4.0 equiv) (Note 9) is added drop-wise *via* syringe pump (Note 10) while maintaining the internal temperature between –78 °C and –75 °C over 2 h (Note 11). The resulting dark brown mixture is allowed to warm to room temperature gradually over 4 h, and stirred for an additional 2 h at room temperature. The mixture is then cooled to 4 °C (ice/water bath), and carefully quenched by the addition of a saturated aqueous NH_4Cl solution (200 mL) after removal of the septum over 30 min. The solid that is formed is dissolved by the addition of de-ionized water (100 mL), and the two phases are separated in a 1-L separatory funnel. The aqueous phase is then further extracted with ethyl acetate (3 × 150 mL). The combined organic phases are washed with brine (50.0 mL), then dried over $MgSO_4$ (30 g, 5 min) and filtered. The filtrate is concentrated by rotary evaporation and further dried under high vacuum for 1 h. The crude product (33.5 g) is purified by flash column chromatography. Thus, the crude brown solid is dissolved in the minimum amount of CH_2Cl_2 (approximately 10 mL), charged on a column (8 × 16 cm) containing 400 g of silica gel (Note 12) and eluted with Et_2O-petroleum ether (5:95, 2 L, then 10:90, 2 L). After the first apolar impurity (this spot is only evident by UV), the title compound elutes, before a mixture of other isomers (Note 13). The combined fractions of the major isomer are concentrated by rotary evaporation to provide a slightly yellow solid (16.8 g). This solid is dissolved in boiling petroleum ether (250 mL), with addition of a small amount of CH_2Cl_2 (5 mL) to complete the dissolution. The solvent is allowed to evaporate to 1/5 of the initial volume at room temperature over 2 days, allowing the crystallisation to occur (Note 14). These crystals are collected by filtration, and rinsed with a small amount (15.0 mL) of cold (0 °C) petroleum ether. Thus, 13.8–14.7 g (40–43%) of pure diamine **2** are obtained (Note 15).

*B. (3aS,7aR)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-hexahydro-isoindole-1,3-dione (**3**).* Into a 250-mL, one-necked, round-bottomed flask, equipped with a septum and a magnetic stirring bar, containing cyclohexanedicarboxylic anhydride (8.50 g, 55.1 mmol, 1.0 equiv) (Note 16) is added glacial acetic acid (100 mL), followed by 2-(3,4-dimethoxyphenyl)ethylamine (10.1 g, 55.4 mmol, 1.0 equiv) (Note 17). The septum is removed and the flask is equipped with a Liebig condenser. The reaction is then heated at reflux (oil bath temperature 120 °C) for 13 h. The resulting mixture is allowed to cool to room temperature and poured into a 1-L beaker containing 400 mL of de-ionized water. The aqueous phase is extracted with diethyl ether (5 × 100 mL). The combined organic phases are transferred into a 1-L Erlenmeyer flask, cooled to 4 °C (water/ice bath) and neutralized by the slow addition (30 min) of a saturated aqueous Na_2CO_3 solution (150 mL) under vigorous stirring. After the addition is finished, the two phases are separated and the organic phase is further washed with saturated aqueous Na_2CO_3 (2 × 50 mL). The organic phase is then dried over anhydrous $MgSO_4$ (20.0 g, 5 min). After removal of the solid by filtration, the organic phase is concentrated by rotary evaporation and further dried under high vacuum for 1 h. The resulting yellow solid is recrystallized from boiling light petroleum ether/ethyl acetate (100 mL:25 mL). Crystallization is allowed to occur at room temperature over 2 h, then at 4 °C overnight. The crystals are collected by filtration and washed with cold (0 °C) petroleum ether (25 mL) to give 14.2 g (81%) (Note 18) of the title compound **3** (Note 19).

*C. (3aS,7aS)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-1,3-dioxo-octahydro-isoindole-3a-carboxylic acid methyl ester (**5**).* Into a 100-mL, two-necked, round-bottomed flask (Note 7), equipped with one septum and one low temperature thermometer, containing a solution of diamine **2** (8.79 g, 20.9 mmol, 1.1 equiv) in THF (50 mL) (Note 20) cooled to –78 °C (dry ice-acetone bath) is introduced *n*-BuLi (8.50 mL, 2.5 M in hexanes, 21.3 mmol, 1.1 equiv) (Note 21) dropwise *via* syringe over 25 min maintaining the internal temperature between –78 °C and –75 °C. The resulting pink solution is allowed to warm to room temperature (23 °C) by removing the cooling bath, and then stirred at this temperature for 30 min (Note 22). This solution is then cooled to –78 °C and transferred over 2 h *via* cannula into a 250-mL two-necked, round-bottomed flask equipped with one septum and one low temperature thermometer containing a solution of imide **3** (6.00 g, 18.9 mmol) in THF (80 mL) while maintaining the internal temperature at –78 °C. The resulting mixture is then stirred for 1 h at –78 °C. A solution of methyl cyanoformate (3.00 mL, 37.8 mmol, 2.0 equiv) (Note 23) in THF (10 mL) is then added dropwise *via* cannula over 15 min. The resulting yellow solution is stirred for 1 h at –78 °C, then the cooling bath is removed, and saturated aqueous $NaHCO_3$ (80.0 mL) is added slowly, followed by de-ionized water (20 mL). The phases are separated, and the aqueous phase is extracted with ethyl acetate (3 × 50 mL). The combined organic phases are washed with brine (50 mL), then dried over $MgSO_4$ (20.0 g, 5 min). After removal of the solid by filtration, the filtrate is concentrated by rotary evaporation. The crude solid residue is dissolved in the minimum amount of CH_2Cl_2 (approximately 15 mL), charged on a column (8 × 16 cm) containing 400 g of silica gel (Note 12) and eluted with ethyl acetate-petroleum ether (30:70, 1 L) to afford recovered diamine **2** (8.40 g, 96%) (Note 24), and then with AcOEt-petroleum ether (50:50, 2 L) to afford title compound **5** (6.20 g, 87 %) (Note 25).

2. Notes

1. The checkers used HPLC grade CH_2Cl_2 purchased from Fisher and passed through two columns of neutral alumina. The submitters used CH_2Cl_2 freshly distilled over CaH_2 under an Ar atmosphere.
2. Glyoxal (40% aqueous solution, ~ 8.8 M) was purchased from Fluka Chemical Company.
3. $MgSO_4$ was purchased from Fisher Company and dried in an oven at 120 °C for 24 h.
4. (*R*)-(+)-Phenylethylamine was purchased from Lancaster Chemical Company {99%, 99% e.e. (HPLC)} and used as received.
5. Throughout this procedure, rotary evaporation refers to a vacuum of 20 mmHg, and high vacuum refers to a vacuum of 1 mmHg.
6. Crude bis-imine (**1**) (R_f = 0.5; petroleum ether:Et_2O 1:1, visualization with $KMnO_4$)
7. The apparatus was dried in an oven (120 °C) overnight and maintained under an atmosphere of dry N_2 during the course of the reaction.
8. The checkers used ACS grade Et_2O stabilized with BHT purchased from Fisher and passed through two columns of neutral alumina. The submitters used anhydrous Et_2O purchased from Fisher Chemicals (water < 0.03%) and purified by pressure filtration under N_2 through activated alumina.
9. Phenylmagnesium chloride was obtained from Aldrich Chemical Company, Inc.

10. The submitters performed this addition via cannula.

11. A white precipitate appeared over the course of the addition.

12. The checkers used silica gel 60A (32- 63D) purchased from Bodman Industries. The submitters used silica gel 60A (35-70µ) purchased from Fluorochem.

13. The ^{1}H NMR of the crude reaction material indicated a ratio of the title compound (1*S*, 2*S*)-**2** to the minor isomer (1*R*, 2*R*)-**2** of 8:2 (R_f (major) = 0.4, (minor) = 0.2, petroleum ether:Et_2O 4:1, visualization with $KMnO_4$). The minor isomer was identified by a characteristic signal at 3.88 ppm in the ^{1}H NMR,[2] and was isolated containing traces of another isomer (3.83 g, brown oil).

14. Alternatively, the solution was simply cooled to room temperature, and then left at 4 °C overnight allowing the crystallisation to occur. After collection of a first batch of crystals, the mother liquor was evaporated to 1/5 of its volume to provide a second batch of crystals.

15. Large colorless crystals. mp = 113–115 °C; $[\alpha]_D^{25}$ +190.0 (*c* = 1.1, $CHCl_3$); FTIR ($CHCl_3$): 3322, 2923, 2859, 1602, 1492, 1454, 1363, 1106, 921, 862 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (d, *J* = 6.6 Hz, 6 H), 2.25 (br s, 2 H), 3.37 (s, 2 H), 3.43 (q, *J* = 6.4 Hz, 2 H), 6.91–7.24 (m, 20 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.5, 55.1, 65.9, 126.7 (**2**), 126.8, 128.0, 128.1, 128.5, 141.8, 145.7; HRMS (ES+) *m*/*z* calcd for $C_{30}H_{33}N_2$ 421.2638, found 421.2644; Found: C, 85.46; H, 7.77; N, 6.64. $C_{30}H_{32}N_2$ requires C, 85.67; H, 7.67; N, 6.66%;

16. Cyclohexanedicarboxylic anhydride (95%) was purchased from Aldrich Chemical Company, Inc.

17. 2-(3,4-Dimethoxyphenyl)ethylamine (98%) was purchased from Alfa Aesar Company.

18. The checkers obtained an 82 % yield when the reaction was run on half-scale.

19. Small white crystals; R_f = 0.4 (petroleum ether:CH_2Cl_2:AcOEt 2:2:1, visualisation with $KMnO_4$); mp = 86.7–88.1 °C; FTIR ($CHCl_3$) 3004, 2922, 2860, 1693, 1514, 1399, 1233, 1150, 1025, 807 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (m, 2 H), 1.37 (m, 2 H), 1.55 (m, 2 H), 1.74 (m, 2 H), 2.72 (m, 2 H), 2.84 (app. t, *J* = 7.7 Hz, 2 H), 3.70 (app. t, *J* = 7.4 Hz, 2 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 6.71–6.76 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 23.6, 32.9, 39.2, 39.6, 55.8, 55.9, 111.2, 112.0, 121.0, 130.3, 147.7, 148.8, 179.7; MS (EI) *m*/*z* 317 (M^+, 28%), 164 ($C_{10}H_{12}O_2$, 28%), 151 ($C_9H_{11}O_2$, 28%). HRMS: found 317.1634, calcd for $C_{18}H_{23}NO_4$ 317.1627.

Found: C, 68.22; H, 7.56; N, 4.40. $C_{18}H_{23}NO_4$ requires C, 68.10; H, 7.31; N, 4.42%.

20. The checkers used HPLC grade THF purchased from Fisher Chemicals and passed though two columns of neutral alumina. The submitters used anhydrous THF purchased from Fisher Chemicals (water < 0.03%) and purified by pressure filtration under N_2 through activated alumina.

21. *n*-BuLi (2.5 M in hexanes) was purchased from Aldrich Chemical Company, Inc.

22. The initial color of this solution varied from orange to pink, and after being stirred at room temperature, from pink to purple.

23. Methyl cyanoformate (99%) purchased from Aldrich Chemical Company, Inc

24. The submitters isolated **2** as small white crystals, $[\alpha]_D^{25}$ +204 (*c* = 1.05, $CHCl_3$).

25. The checkers obtained an 81% yield when the reaction was run on half-scale. $[\alpha]_D^{25}$ –52.9 (*c* = 1.1, $CHCl_3$). The submitters obtained an optical rotation of $[\alpha]_D^{25}$ –62.0 (*c* = 1.1, $CHCl_3$). R_f = 0.4 (petroleum ether:CH_2Cl_2:AcOEt 2:2:1, visualization with $KMnO_4$); FTIR ($CHCl_3$) 2940, 1742, 1701, 1515, 1349, 1234, 1026, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (m, 1 H), 1.30–1.37 (m, 3 H), 1.48–1.60 (m, 2 H), 1.98 (ddd, *J* = 14.2, 8.5, 4.2 Hz, 1 H), 2.26 (m, 1 H), 2.86 (app. td, *J* = 7.7, 2.2 Hz, 2 H), 3.19 (dd, *J* = 6.5, 3.7 Hz, 1 H), 3.72 (s, 3 H), 3.73 (m, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 6.69–6.75 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.5, 20.8, 21.4, 28.5, 32.7, 39.8, 43.8, 53.3, 54.1, 55.9, 56.0, 111.1, 112.0, 121.1, 129.9, 147.8, 148.9, 170.2, 176.1, 177.6; MS (FAB) *m/z* 375 (M^+, 100%), 164 ($C_{10}H_{12}O_2$, 90%), 151 ($C_9H_{11}O_2$, 35%); HRMS: found 375.1683, calcd for $C_{20}H_{25}NO_6$ 375.1682. Found: C, 63.69; H, 6.75; N, 3.65. $C_{20}H_{25}NO_6$ requires C, 63.99; H, 6.71; N, 3.73. The ee was determined as 86–88% by HPLC (OD column, EtOH:hexanes 10:90, 0.6 mL/min), the retention times were 22.5 min (major) and 27 min (minor). The submitters determined the ee was 93–95% by HPLC (OD column, EtOH:hexanes 10:90, 0.6 mL/min), the retention times were 35 min (major) and 47 min (minor).

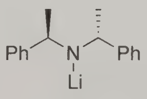
Waste Disposal Information

All toxic materials were disposed of in accordance with "Destruction of Hazardous Chemicals in the Laboratory"; Lunn, G.; Sansone, E.B. 2nd Ed.; John Wiley & Sons, Inc.

3. Discussion

Over the past two decades, the use of chiral lithium amide bases in synthesis has become widespread, enabling the synthesis of chiral building blocks with high selectivity.[3] The three main classes of reactions where chiral lithium amide bases have been applied successfully are: (i) deprotonation of prochiral cyclic ketones, (ii) rearrangement of epoxides to allylic alcohols, and (iii) aromatic and benzylic functionalization of tricarbonyl (η^6-arene)chromium complexes. In all these examples, the chiral base selects between enantiotopic protons in kinetically controlled deprotonations of achiral or prochiral substrates. Another fundamentally different process also exists, in which the chiral lithium amide base first acts as a strong base to produce a prochiral carbanion, e.g. an enolate. The stereochemical outcome of the subsequent reaction of the anion with an electrophile is then controlled by the complexed chiral secondary amine. More recently, catalytic variants of some of the reactions described above have emerged. In this case, a substoichiometric amount of the chiral base is used in conjunction with a stoichiometric amount of an achiral base.[4]

The procedure described herein illustrates the efficient use of a chiral lithium amide base to mediate desymmetrization of a prochiral cyclic imide. Imide **5** has been used successfully in a synthesis of the proposed structure of the alkaloid Jamtine.[5] Apart from chiral diamine **2**, commercially available bisphenylethylamine in the form of its lithium amide **6** has been used for the desymmetrization of certain imides.[6] However, in many cases chiral base **2** has been shown to provide better selectivity. For example, in the case of imide **9** (Table 1, entry 2), the use of lithium amide **6** proved less selective, providing **9** in only 70% ee. It is also noteworthy that **2** can be used as its mono-lithiated form **4**, or as its bis-lithiated derivative **7**, both species leading to high enantioselectivities. Table 1 gives examples of other types of imides that have been successfully desymmetrized using chiral base **7**.



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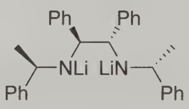


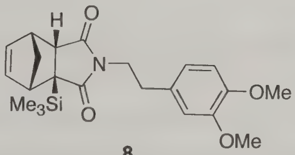
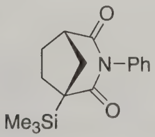
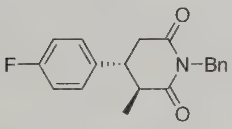
7

Chiral diamine **2** has also been found to be useful for the desymmetrization of prochiral ketones,[7] piperidines,[8] various tricarbonyl(η^6-arene)chromium complexes,[9] asymmetric rearrangement of episulfoxides,[10] asymmetric thia-Sommelet dearomatization,[11] and asymmetric hydrosilylation[12] with good to excellent levels of enantioselectivities.

The synthesis of diamine **2** suffers from a somewhat low yield; however, it can be easily prepared in large scale.[13] Moreover, it can easily be recovered in essentially pure form by column chromatography after the reaction. Two alternative syntheses of **2** have been reported, either using phenyl lithium instead of a Grignard derivative[2] or *via* pinacol coupling of imines.[14] Neither of these methods, however, provided better yields of the product.

In summary, the chiral base desymmetrization of imides provides an efficient method to access highly functionalised molecules with high enantioselectivities. This strategy has been applied to the synthesis of natural products,[5,15,17] as well as a drug molecule.[17]

Table 1: Examples of Imide Desymmetrization using Base **7**.

Entry	Electrophile	Conditions	Product	Yield	ee
1[15]	TMSCl	THF, –78 °C	 **8**	82%	92–94%
2[16]	TMSCl	THF, –105 °C LiCl	 **9**	47%	94%
3[17]	MeI	THF, –78 °C	 **10**	65%	97%

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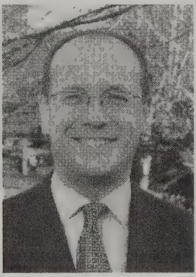
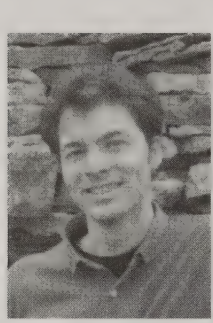
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*R*)-(+)-Phenylethylamine: Benzenemethanamine, α-methyl-, (αR)-; (3886-69-9)
Aqueous glyoxal solution: Ethandial; (107-22-2)
Phenylmagnesium chloride: Magnesium, chlorophenyl-; (100-59-4)
1(*S*),2(*S*)-Diphenyl-*N*,*N'*-bis-[1(*R*)-phenyl-ethyl]-ethane-1,2-diamine; (156730-49-3)
Cyclohexanedicarboxylic anhydride: 1,3-Isobenzofurandione, hexahydro-; (85-42-7)
2-(3,4-Dimethoxyphenyl)ethylamine: Benzeneethanamine, 3,4-dimethoxy-; (120-20-7)
(3a*S*,7a*R*)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-hexahydro-isoindole-1,3-dione : 1H-Isoindole-1,3(2H)-dione, 2-[2-(3,4-dimethoxyphenyl)ethyl]-hexahydro-, (3aR,7aS)-rel-; (501085-17-2)
Butyllithium; (109-721-8)
Methyl cyanoformate: Carbonocyanidic acid, methyl ester (9CI); (17640-15-2)
(3a*S*,7a*S*)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-1,3-dioxo-octahydro-isoindole-3a-carboxylic acid methyl ester; (501085-21-8)

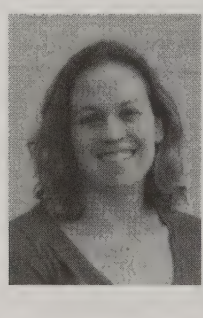


Nigel Simpkins was born in 1959 in Luton, England. He completed both his undergraduate studies and his Ph.D (with S. V. Ley) at Imperial College, London. He spent one year with K. C. Nicolaou (Philadelphia) before taking his first lectureship position at Queen Mary College, University of London. In 1988 he moved to the University of Nottingham where he was promoted to professor in 1995. From 2007 he will be Haworth Professor of Chemistry at the University of Birmingham. His research interests include the use of chiral base reagents in synthesis, and the total synthesis of bioactive natural products.

Fengzhi Zhang received his B.S. degree in 2000 and M.S. degree in 2003 from Lanzhou University, China where he worked on marine natural product synthesis with Professor Yulin Li. He then worked as a medicinal chemist in a pharmaceutical company in Shanghai until entering the Ph.D. program with an Overseas Research Scholarship at the University of Nottingham in 2004. Under the guidance of Professor Nigel Simpkins his research focuses on the asymmetric synthesis of erythrinan alkaloids.

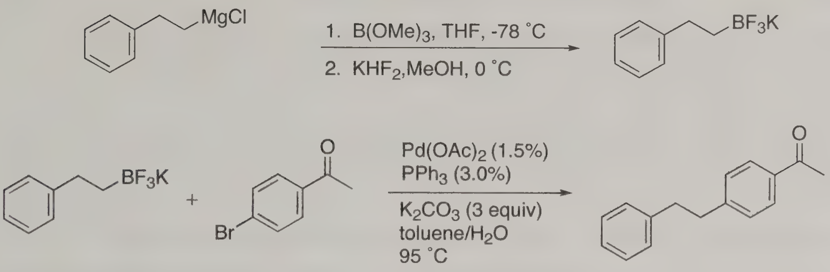


Vincent Rodeschini graduated from the School of Chemistry of Mulhouse in 2001. In 2004, he received his PhD from the Université de Haute Alsace, working under the supervision of Prof. Jacques Eustache on the synthesis of angiogenesis inhibitors. He then moved to the UK as a Marie Curie Postdoctoral Fellow at the university of Nottingham, under the mentorship of Prof. Nigel Simpkins (2005-2007). His research was focused on the use of bridgehead lithiation to construct bridgehead substituted natural products. In 2007, he joined the pharmaceutical company Novexel, Paris, as a medicinal chemist in the field of antibiotics.



Melissa A. Beenen grew up in Oregon and received her BA in chemistry at Northwestern University in 2004. She then began her doctoral studies at the University of California, Berkeley in the laboratories of Professor Jonathan A. Ellman. Her graduate research has focused on the metal-catalyzed asymmetric synthesis of amines using *N-tert*-butanesulfinamde.

1-(4-ACETYLPHENYL)-2-PHENYLETHANE from POTASSIUM 2-PHENETHYLTRIFLUOROBORATE and 4-BROMOACETOPHENONE



Submitted by Gary A. Molander and Daniel E. Petrillo.[1]
Checked by Scott E. Denmark and Christophe Eggertswyler.

1. Procedure

A. Preparation of Potassium 2-Phenethyltrifluoroborate. A single-necked, 500-mL round-bottomed flask, equipped with a magnetic stirring bar, a 125-mL pressure-equalizing addition funnel, and connected by a three-way stopcock fitted with a rubber septum to a vacuum-argon manifold, is flame-dried under vacuum (0.3 mm Hg), then is flushed with dry argon. THF (90 mL) is added via syringe to the addition funnel, followed by trimethyl borate (10.0 mL, 89.2 mmol, 1.5 equiv) (Note 1). After the addition of the trimethyl borate to the round-bottomed flask, additional THF (30 mL) (Note 1) is added via syringe to rinse the addition funnel. The solution is then cooled in a dry ice/isopropyl alcohol bath. Phenethylmagnesium chloride (60.0 mL of a 1.0 M solution in THF, 60.0 mmol) (Note 2) is then added dropwise over 1 h via the addition funnel. The mixture is stirred in the dry ice/isopropyl alcohol bath for 1.5 h, then is allowed to warm to room temperature over 1 h. The resulting white slurry is then cooled in an ice/water bath and methanol (60 mL) (Note 3) is charged into the addition funnel by syringe. The methanol is added over 15 min to dilute the slurry (Note 4). The argon inlet is removed and a solution of potassium hydrogen fluoride (80.0 mL of 4.5 M aqueous solution, 360 mmol, 6.0 equiv) (Note 5) is then charged into the addition funnel and is

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added dropwise over 15 min. The resulting solution is stirred for 1 h in the ice/water bath, and then is concentrated on a rotary evaporator (60 °C water bath, 9 mm Hg). The resulting white solids are placed on a high-vacuum line (0.3 mm Hg) for 36 h until the solids appear dry (Note 6). Acetone (120 mL) (Note 7) is added and the solids are broken up into a fine powder with a spatula. The suspension is then placed on a rotary evaporator and heated (40 °C) with rotation under atmospheric pressure for 5–10 min and filtered over a 14 g pad of Celite in a glass-fritted filter funnel. Acetone (120 mL) is added to the solid remaining in the flask, the suspension is placed on a rotary evaporator and heated (40 °C) with rotation under atmospheric pressure for 5–10 min and filtered over the same Celite pad. This process is repeated one additional time (Note 8). The combined filtrates are concentrated on a rotary evaporator (60 °C water bath) to a white solid, which is dissolved in a minimal amount of dry acetone (~25 mL). Diethyl ether (30 mL) is then added to precipitate the product. The white slurry is allowed to cool first to 23 °C, and then is cooled in an ice/water bath for 15 min. The slurry is placed in a refrigerator (4 °C) for 1 h, and is then filtered to give 9.84 g (77%) of a white solid (Note 9).

B. Preparation of 1-(4-Acetylphenyl)-2-phenylethane. A three-necked, 250-mL, round-bottomed flask, equipped with a reflux condenser, a rubber septum, a glass stopper, a magnetic stirring bar, and connected to a vacuum-argon manifold, is charged sequentially with potassium 2-phenethyltrifluoroborate (7.77 g, 36.6 mmol, 1.05 equiv), 4-bromoacetophenone (6.97 g, 35.0 mmol), potassium carbonate (14.5 g, 105 mmol, 3.0 equiv), triphenylphosphine (0.275 g, 1.05 mmol, 0.03 equiv) and palladium acetate (0.118 g, 0.53 mmol, 0.015 equiv) (Note 10). The flask is evacuated and filled with dry argon three times. Toluene (105 mL) (Note 11) and H_2O (21 mL) are added, and the resulting two-phase mixture is stirred in a 95 °C oil bath until consumption of the 4-bromoacetophenone is indicated by GC analysis (Note 12). The mixture is cooled to room temperature and then is transferred to a 250-mL separatory funnel. The flask is rinsed with toluene (20 mL) and H_2O (20 mL). The layers are shaken and separated. The organic layer is washed with 10% aq. citric acid solution (20 mL) (Note 13) and saturated aq. NaCl solution (20 mL). The organic layer is dried over anhydrous Na_2SO_4 (0.780 g) and filtered through a medium porosity glass-fritted funnel, rinsing the drying agent with toluene (20 mL). The resulting solution is concentrated (50 °C water bath, 9 mmHg) to a light yellow solid (Note 14), which is crystallized from methanol to give 5.79 g

(74%, two crops) (Notes 15, 16) of a light tan solid. Recrystallization of 0.3 g of this solid from hot methanol (2 mL) provided white, crystalline material (0.25 g) of analytical purity (Note 17).

2. Notes

1. Trimethyl borate (98%) was obtained from Aldrich Chemical Company and was distilled from sodium. THF (Fischer, HPLC Grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 (a supported copper catalyst for removing oxygen) under a positive pressure of argon.

2. Phenethylmagnesium chloride (1.0 M in THF) was obtained from Aldrich Chemical Company and was used as received.

3. Methanol (ACS Grade) was obtained from Aldrich Chemical Company and was distilled continuously from $Mg(OMe)_2$.

4. At this stage the solution may be transferred to a Nalgene vessel to avoid etching of the glass flask by the KHF_2.

5. Potassium hydrogen fluoride (p.a. >99%) was obtained from Fluka and was used as received.

6. Care was taken to ensure that the solids are free of water or else inorganic fluoride contaminated the final product.

7. Acetone (Spectroscopic Grade) was obtained from Aldrich Chemical Company and was used as received. Diethyl ether (ACS Grade) was obtained from Fischer Scientific and was used as received.

8. The desired product was soluble in acetone whereas the inorganic salts were not. This extractive process ensured that any product trapped within the inorganic solids would be dissolved.

9. Analytical data: mp: 332–335 °C (sealed tube). IR cm^{-1}: 3026, 2921, 2847; ^1H NMR (600 MHz, acetone-d^6) δ: 0.51 (br, 2 H), 2.56 (dt, *J* = 8.8, 4.7 Hz, 2 H), 7.00–7.05 (m, 1 H), 7.14–7.17 (m, 4 H); ^{13}C NMR (150 MHz, acetone-d^6) δ: 32.1, 124.5, 127.9, 128.0, 148.5; ^{11}B NMR (192.4 MHz, acetone-d^6) δ 5.48; ^{19}F NMR (470 MHz, acetone-d^6) δ –142.32; MS (ES): *m/z* 173.1 (100) Anal. Calcd for $C_9H_9BF_3K$: C, 45.31; H, 4.28; F, 26.88. Found: C, 45.03; H, 4.29; F, 25.38.

10. 4-Bromoacetophenone (98%) was obtained from Aldrich Chemical Company and was used as received. Potassium carbonate (ACS Grade) was purchased from Fisher Scientific and was used as received. Triphenylphosphine (ReagentPlus Grade, 99%) was obtained from Aldrich

Chemical Company and was used as received. Palladium acetate was obtained from Frontier Scientific and was used as received.

11. Toluene (ACS Grade, 99.5+%) was obtained from Aldrich Chemical Company and was used as received.

12. The reaction was assayed as follows: an aliquot (20 μL) was removed and filtered through a small pad of silica gel in a Pasteur pipette, rinsing with EtOAc (1.5 mL). The sample was then injected on an HP 5890 GC with an HP 1 column (100 °C for 1 min., ramp to 250 °C at 25 °C/min.). Typical retention times were: 4-bromoacetophenone: 4.1 min, 1-(4-acetylphenyl)-2-phenylethane: 7.4 min. The reaction generally required 16–20 h.

13. Citric acid monohydrate (Baker Analyzed Reagent) was obtained from J. T. Baker Chemical and was used as received.

14. The submitters found that the crude product was a dark yellow solid that needed to be decolorized with activated carbon in MeOH prior to recrystallization.

15. The crude product was slurried in MeOH (25 mL) in a 100-mL flask and heated to 50 °C in an oil bath. After dissolution, the solution was allowed to cool to room temperature. It was then placed in an ice/water bath for 1 h, after which crystals were removed by filtration. The filtrate was concentrated (50 °C water bath) to ~ 10 mL and cooled to 0 °C, after which a second crop of the crystals was collected via filtration. This material had a melting point of 66–68 °C.

16. The submitters noted that the product may also be purified by silica gel column chromatography (10% EtOAc/hexanes as eluent, $R_f = 0.34$) to give an 89% yield of product of unspecified purity.

17. Analytical data: mp: 68–72 ºC (lit. mp: 68–70 ºC).[2] IR cm^{-1}: 1676, 1601; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.58 (s, 3 H), 2.92–3.01, (m, 4 H), 7.15-7.30 (m, 7 H), 7.88 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 26.5, 37.3, 37.8, 126.1, 128.3, 128.4, 128.5, 128.7, 135.1, 141.0, 147.4, 197.7. MS (EI, 70 eV): *m/z* 224 (M^+, 44), 209 (12), 181 (8), 133 (12), 105 (8), 91 (100), 65 (7); Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.59; H, 7.31.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The metal-catalyzed cross-coupling reaction between organometallic reagents with electrophiles has emerged as one of the most powerful methods for carbon-carbon bond formation.[3] The Suzuki-Miyaura[4] reaction using organoboron reagents is among the most important, due its tolerance of a broad range of functional groups as well as its formation of non-toxic byproducts. The use of alkylboron reagents has received special attention because of their utility in natural product synthesis.[5]

The coupling of alkylboron reagents has generally been performed with trialkylboranes (R_3B), alkylborinate esters (R_2BOR'), alkylboronic acids [$RB(OH)_2$] or boronate esters [$RB(OR')_2$]. Trialkylboranes such as 9-BBN[6] derivatives are among the most common, although they present problems such as functional group intolerance, air sensitivity, and a lack of atom economy. The use of alkylboronate esters often results in low yields in coupling reactions unless highly toxic thallium bases are used.[7] Additionally, these species are often hydrolytically unstable. The coupling of alkylboronic acids[8] has shown more promise, although their tendency to form cyclic anhydrides (boroxines) often makes determining their precise stoichiometry difficult.

Recently, potassium organotrifluoroborates (RBF_3K) have been shown to be highly effective coupling partners in the Suzuki-Miyaura reaction.[9] They are easily prepared on large-scale (>200 g) by the addition of KHF_2 (an inexpensive fluoride source) to various organoboron reagents such as boronic acids, boronate esters, and organodihaloboranes. Their advantages over traditional organoboron reagents include their greater nucleophilicity, air stability, and atom economy. Initial reports described their use in the palladium-catalyzed coupling with arenediazonium[10] or diaryliodonium[11] salts. Previous reports from our laboratory have shown the successful cross-coupling of potassium alkyl-,[12] alkenyl-,[13] aryl-,[14] and alkynyltrifluoroborates[15] with aryl- and alkenyl halides as well as triflates using catalytic $PdCl_2(dppf) \cdot CH_2Cl_2$ and Cs_2CO_3 or Et_3N as a base. In the case of aryltrifluoroborates, it was also shown that ligandless conditions using $Pd(OAc)_2$ and K_2CO_3 can be used.[16] Batey and Quach have reported similar cross-coupling reactions using tetraalkylammonium trifluoroborates.[17] Recently, functionalized organotrifluoroborates such as epoxidized[18] and dihydroxylated[19] potassium alkyltrifluoroborates have been coupled to electrophiles under palladium catalysis. The procedure described above represents a typical coupling reaction in which a commercially available, easily-handled potassium alkyltrifluoroborate is coupled to a common aryl electrophile.

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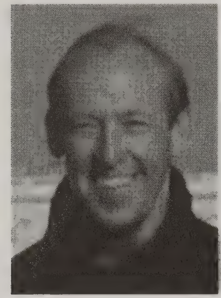
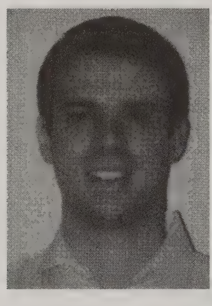
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Trimethyl borate; (121-43-7)
Phenethylmagnesium chloride: Magnesium, chloro(2-phenylethyl)-; (90878-19-6)
Potassium hydrogen fluoride: (7789-29-9)
Potassium 2-phenethyltrifluoroborate: Borate(1-), trifluoro(2-phenylethyl)-, potassium, (T-4)-: (329976-74-1)
4-Bromoacetophenone: Ethanone, 1-(4-bromophenyl)-: (99-90-1)
Triphenylphosphine; (603-35-0)
Palladium acetate; (3375-31-3)

1-(4-Acetylphenyl)-2-phenylethane: 1-[4-(2-Phenylethyl)phenyl]-ethanone; (785-78-4)



Professor Gary Molander received his B.S. degree at Iowa State University in 1975, working with Professor Richard C. Larock. He obtained his Ph.D. degree in 1979 under the direction of Professor Herbert C. Brown. He joined Professor Barry Trost's group at the University of Wisconsin, Madison as a National Institutes of Health postdoctoral fellow in 1980, and in 1981 he accepted an appointment at the University of Colorado, Boulder. In 1999 he joined the faculty at the University of Pennsylvania. His research interests focus on the development of new synthetic methods for organic synthesis and natural product synthesis.

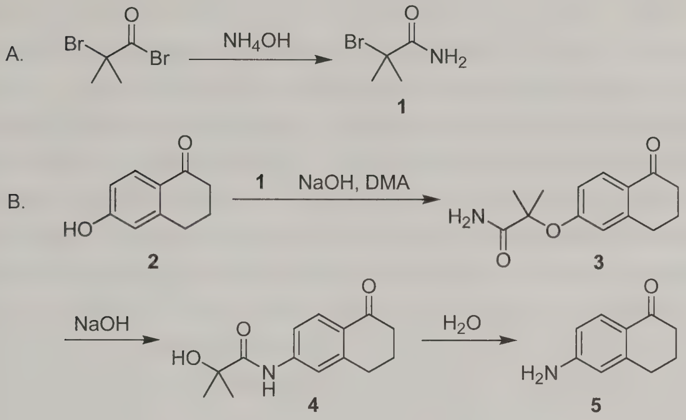


Daniel E. Petrillo received an A.B. in chemistry with honors from Princeton University in 1999. His senior thesis research was conducted in the laboratory of Professor Martin F. Semmelhack. From 1999 to 2002 he was employed as a chemist in the department of Process Research at Merck. He then entered graduate school at the University of Pennsylvania where his research has centered on synthetic methods using organotrifluoroborates under the guidance of Professor Gary A. Molander.

Christophe Eggertswyler was born and raised in Switzerland. He received his Diploma In Chemistry from the University of Fribourg, where he performed undergraduate research on the synthesis and ab initio computation of vibrational optical activity of sulfoxides. After graduation, he decided to stay in Fribourg where he joined the research group of Professor Titus A. Jenny. He investigated the synthetic potential of new iron tricarbonyl complexes in an organometallic approach to the taxane skeleton synthesis. After completion of his Ph.D. thesis in 2004, he joined the research group of Professor Scott E. Denmark at the University of Illinois at Urbana Champaign in 2005 as a postdoctoral research associate. His research focuses on the mechanistic study of the transmetallation event in cross-coupling reactions.

A NEW PRACTICAL ONE-POT CONVERSION OF PHENOLS TO ANILINES: 6-AMINO-3,4-DIHYDRO-1(2*H*)-NAPHTHALENONE

[1(2*H*)-Naphthalenone, 6-amino-3,4-dihydro-]



Submitted by Masahiro Mizuno[1] and Mitsuhisa Yamano.[1]
Checked by Jun Takeuchi and Jonathan A. Ellman.

1. Procedure

A. 2-Bromo-2-methylpropanamide (1): A 250-mL, three-necked, round-bottomed flask, fitted with a thermometer, pressure-equalizing dropping funnel and equipped with a mechanical stirrer is charged with 28.0 -30.0% aqueous ammonium hydroxide (35.7 mL, approximately 600 mmol) (Note 1) and water (44.3 mL). The dropping funnel is charged with 2-bromo-2-methylpropanoyl bromide (50.0 g, 217.5 mmol) (Note 1), and the mixture is cooled below 5 °C (internal temperature) using a brine/ice bath with stirring. The 2-bromo-2-methylpropanoyl bromide is added dropwise slowly with stirring so that the internal temperature does not rise above 15 °C with cooling using a brine/ice bath (Caution: Exothermic reaction!). Stirring is continued for 1 h after the addition is complete, with the temperature of the reaction mixture maintained between 0 and 5 °C. The resulting white precipitate is collected by filtration on a glass filter funnel and washed three times with 40 mL of water to give **1** (33.0-33.5 g, 91.4-93.8 %) as a white crystalline powder (Note 2).

Org. Synth. **2007**, *84*, 325-333
Published on the Web 5/17/07

B. 6-Amino-3,4-dihydro-1(2H)-naphthalenone (5): A 500-mL, three-necked, round-bottomed flask, fitted with a reflux condenser, thermometer, addition funnel and equipped with a large magnetic stirring bar is charged with 3,4-dihydro-6-hydroxy-1(2*H*)-naphthalenone (**2**) (10.0 g, 61.7 mmol) (Note 1) and *N*,*N*-dimethylacetamide (90 mL) (Note 1). Sodium hydroxide (7.40 g, 185 mmol) (Note 1) is added into the flask by temporarily removing the addition funnel and the resulting mixture is stirred at 20–30 °C (Note 3) for 1 h. 2-Bromo-2-methylpropanamide (**1**) (30.7 g, 185 mmol) is added to the reaction mixture (Note 4) through the addition funnel, and the resulting mixture is stirred at 25–35 °C (Note 3) for 5 h. After the reaction period (Note 5), sodium hydroxide (22.2 g, 555 mmol) is added, and the resulting mixture is stirred for 1 h with heating to 50–60 °C (internal temperature) using an oil bath. After the reaction period (Note 6), water (90 mL) is added by use of an addition funnel, and the mixture is heated at reflux using an oil bath for 1 h (internal temperature is 85–95 °C). Water (180 mL) is added to the reaction solution using an addition funnel, and the resulting precipitated mixture is allowed to cool slowly to 20–30 °C. The precipitated crystalline powder is collected by filtration on a glass filter funnel (Note 7) and washed three times with 90 mL of water to give **5** (6.28 g, 63.2%) as a brown crystalline powder (Notes 8 and 9).

2. Notes

1. 2-Bromo-2-methylpropanoyl bromide and 3,4-dihydro-6-hydroxy-1(2*H*)-naphthalenone (**2**) were purchased from Aldrich Chemical Company, Inc. The submitters purchased 25–27.9% aqueous ammonium hydroxide, *N*,*N*-dimethylacetamide and sodium hydroxide from Wako Pure Chemical Industries, Ltd. The checkers purchased *N*,*N*-dimethylacetamide and sodium hydroxide from Aldrich Chemical Company, Inc. The checkers purchased 28.0 – 30.0% aqueous ammonium hydroxide from EMD Chemicals, Inc. All of the reagents were used without further purification.

2. 2-Bromo-2-methylpropanamide (**1**) showed the following physical data: mp 146–148 °C; IR (film): 3382, 3187, 1652, 1625, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97 (s, 6 H), 6.20 (br, 1 H), 6.60 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.3, 61.1, 174.9; MS (EI): *m/z* 167 (3), 165 (3), 123 (23), 121 (23), 86 (100); Anal. Calcd. for C_4H_8BrNO: C, 28.94; H, 4.86; N, 8.44; Br, 48.13. Found: C, 28.71; H, 4.96; N, 8.33. The submitters reported that HPLC analysis was performed on YMC-Pack

ODS-A302 column (150 mm×4.6 mm i.d.) with 50 mM aqueous KH_2PO_4 solution-MeCN (65:35) at 25 °C. Detected at 254 nm(UV) t_R: 2.7 (area 100.0%)

3. After the addition of the reagents, the internal temperature gradually rose to approximately 30 °C and then over time returned to ambient temperature.

4. This reaction was slightly endothermic.

5. Although the alkylation reaction was not complete after 5 h, the procedure could be continued with no problem. The submitters reported that the intermediate formed at this stage, 2-methyl-2-[(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]propanamide (**3**), can be isolated without further purification by the addition of water to the reaction mixture. Intermediate **3** isolated by the submitters in this fashion showed the following physical data: HPLC (YMC-Pack ODS-A302 column (150 mm x 4.6 mm i.d.) with 50 mM aqueous KH_2PO_4 solution-MeCN (80:20) at 25 °C. Detected at 254 nm (UV)) t_R: 4.5(**1**), 11.1(**2**), 20.4(**3**, area 99.4%); mp 117.5-119.5 °C; IR (KBr): 3357.5, 3164.6, 1687.4, 1664.3, 1604.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.61 (s, 6 H), 2.12 (quint, J = 6.1 Hz, 2 H), 2.61 (t, J = 6.2 Hz, 2 H), 2.91 (t, J = 6.1 Hz, 2 H), 5.65 (br, 1 H), 6.41 (br, 1 H), 6.75 (d, J = 2.3 Hz, 1 H), 6.84 (dd, J = 8.6 Hz, 2.4Hz, 1 H), 7.98 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7, 25.5(2C), 30.4, 39.3, 81.8, 118.7, 119.0, 128.1, 129.6, 146.9, 159.2, 177.4, 197.6; MS (EI): *m/z* 247 $[M]^+$; Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.71; H, 6.76; N, 5.71.

6. The submitters reported that this intermediate, 2-hydroxy-2-methyl-*N*-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)propanamide (**4**), can be isolated without further purification by the addition of water to the reaction mixture. Intermediate **4** isolated by the submitters in this fashion showed the following physical data: HPLC (YMC-Pack ODS-A302 column (150 mm x 4.6 mm i.d.) with 50 mM aqueous KH_2PO_4 solution-MeCN (80:20) at 25 °C. Detected at 254 nm (UV)) t_R: 4.5(**1**), 11.1(**2**), 17.7(**4**, area 99.6%), 20.4(**3**); mp 162.5-163 °C; IR (KBr): 3305.4, 1672.0, 1600.6, 1540.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 6 H), 2.14 (quint, J = 6.2 Hz, 2 H), 2.65 (t, J = 6.2 Hz, 2 H), 2.73(s, 1 H), 2.96 (t, J = 6.2 Hz, 2 H), 7.31 (dd, J = 8.5, 2.1 Hz, 1 H), 7.78 (d, J = 1.6 Hz, 1 H), 8.01 (d, J = 8.5 Hz, 1 H), 8.90 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3, 27.8(2C), 30.0, 39.0, 74.2, 117.6, 118.4, 128.6, 128.7, 142.1, 146.4, 175.1, 197.8; MS (FAB): *m/z* 248 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00;

H, 6.93; N, 5.66. Found: C, 68.19; H, 7.06; N, 5.64.

7. After the reaction mixture was stirred for 14 h, the checkers collected the precipitated crystalline powder.

8. The checkers obtained a 60.4% yield when the reaction was run on half-scale. 6-Amino-3,4-dihydro-1(2*H*)-naphthalenone (**5**) showed the following physical data: mp 128–130 °C; IR(film): 3423, 3349, 3239, 1567, 1553, 1356, 1325, 1292 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.05 (quint, $J = 6.4$ Hz, 2 H), 2.56 (t, $J = 6.4$ Hz, 2 H), 2.81 (t, $J = 6.4$ Hz, 2 H), 4.28 (br, 2 H), 6.41 (d, $J = 2.0$ Hz, 1 H), 6.53 (dd, $J = 8.4, 2.0$ Hz, 1 H), 7.87 (d, $J = 8.4$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.2, 29.9, 38.7, 112.3, 113.0, 123.6, 129.6, 147.0, 151.4, 197.0; MS (EI): *m/z* 161 (76, $[M]^+$), 133 (100), 105 (28); Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.24; H, 6.93; N, 8.67.

9. The submitters reported the isolation of an off-white crystalline powder. The submitters reported that HPLC analysis was performed on a YMC-Pack ODS-A302 column (150 mm x 4.6 mm i.d.) with 50 mM aqueous KH_2PO_4 solution-MeCN (80:20) at 25 °C. Detected at 254 nm (UV) t_R: 4.5(**1**), 8.6(**5**, area 100.0%), 11.1(**2**), 17.7(**4**), 20.4(**3**).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since more phenols are generally more available than the corresponding anilines, several methods have been developed for the direct conversion of phenols to anilines.

These methods include the Bucherer reaction[2] and activation of phenols with 4-chloro-2-phenylquinazoline [3] or diethyl chlorophosphate;[4] however, all of these methods suffer from drawbacks. The Bucherer reaction is restricted to naphthalenes and related heterocycles, whereas benzene derivatives are much less reactive. Rearrangement of aryloxyquinazoline, prepared from 4-chloro-2-phenylquinazoline, requires extremely high temperatures (approximately 300 °C) and strongly basic conditions. Preparation of aryl diethyl phosphate esters requires the use of toxic diethyl chlorophosphate and potassium metal in liquid ammonia.

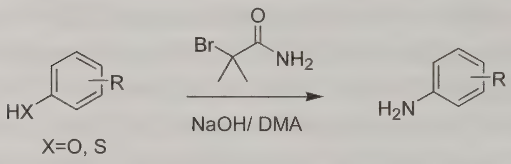
Another method, which has been used for the conversion of phenols to anilines, is an alkylation-Smiles rearrangement-hydrolysis[5] sequence. However, this method also has some disadvantages. The three-step process requires the use of sodium hydride and *N*,*N*-dimethylformamide, which has the risk of causing an exothermic, uncontrollable reaction.[6]

Recently, palladium-catalyzed amination of aryl sulfonates, e.g., aryl triflates and aryl nonaflates, has been investigated.[7] However, this method requires that aryl sulfonates be synthesized from the corresponding phenols. The high cost of palladium and the potential for metal contamination of the final product are issues associated with this method.

6-Amino-1-tetralone (**5**), which is an important synthetic intermediate, has been synthesized by two general synthetic methods. The first of these involves a Friedel-Crafts ring-closure step near the end of the synthetic sequence. The starting material, β-benzoylpropionic acid, was nitrated to give the *meta*-nitro compound, which was then reduced to provide the amine. Acetylation of the amino group and hydrogenolysis of the ketone carbonyl generated the acetamido acid. Friedel-Crafts cyclization provided 6-acetamido-1-tetralone, which was hydrolyzed to aniline **5**.[8] An alternative synthetic method involved the introduction of the ketone carbonyl into the saturated side chain as a key step. The tetralin starting material was acetylated to give 6-acetyltetralin, which then was converted to the oxime. Beckmann rearrangement of the oxime gave 6-acetamidotetralin. Selective oxidation gave 6-acetamido-1-tetralone, which was hydrolyzed to aniline **5**. 8b, 9

These two general methods required many steps to produce aniline **5**. Our novel three-step, one-pot Smiles rearrangement process[10] is a practical and useful alternative route to this compound.

ONE-POT CONVERSION OF PHENOLS (THIOPHENOLS) TO ANILINES



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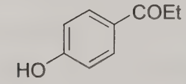
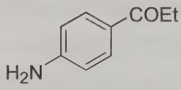
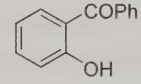
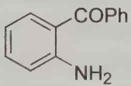
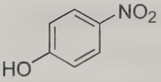
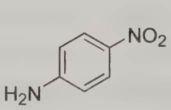
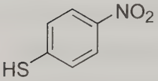
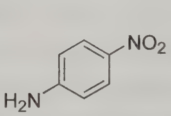
1			92	86
2			72	77
3			83	38
4			99	49

[a] Conversion based on quantitative HPLC analysis (not optimized)

[b] Isolated yield (products separated as crystals from reaction mixture by filtration)

References and Notes

1. Chemical Development Laboratories, Pharmaceutical Production Division, Takeda Pharmaceutical Company Limited., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka, 532-8686, Japan., Mizuno_Masahiro@takeda.co.jp.

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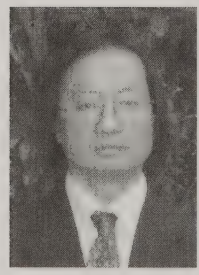
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6-Amino-3,4-dihydro-1(2*H*)-naphthalenone, 6-amino-1-tetralone:

1(2*H*)-Naphthalenone, 6-amino-3,4-dihydro-; (3470-53-9)
2-Bromo-2-methylpropanamide: Propanamide, 2-bromo-2-methyl-; (7462-74-0)
2-Bromo-2-methylpropanoyl bromide: Propanoyl bromide, 2-bromo-2-methyl-; (20769-85-1)
3,4-Dihydro-6-hydroxy-1(2*H*)-naphthalenone, 6-hydroxy-1-tetralone: 1(2*H*)-Naphthalenone, 3,4-dihydro-6-hydroxy-; (3470-50-6)
2-Methyl-2-[(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]propanamide: Propanamide, 2-methyl-2-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)oxy]-; (418761-91-8)
2-Hydroxy-2-methyl-*N*-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)propanamide: Propanamide, 2-hydroxy-2-methyl-*N*-(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)-; (418761-92-9)

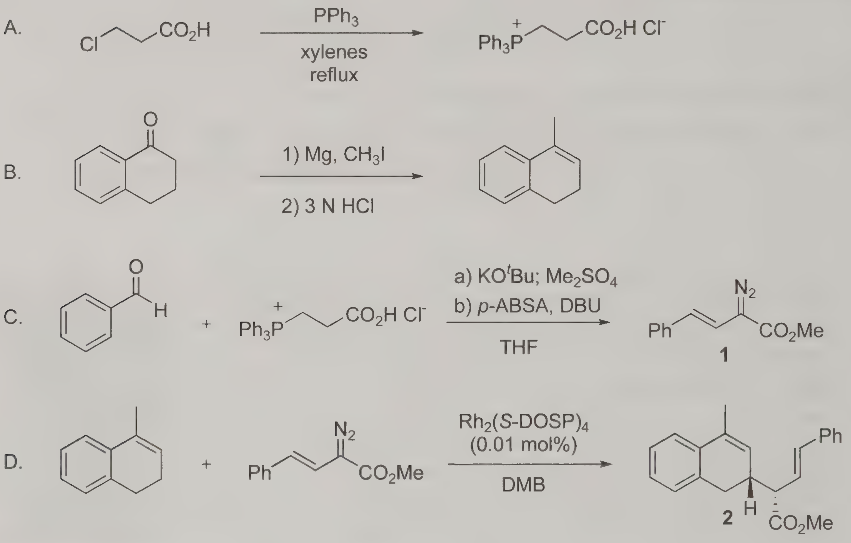
Masahiro Mizuno was born in 1965 in Shiga, Japan. After he received his M.S. in 1990 under Professor Mikio Hori from Gifu Pharmaceutical University, he joined Takeda Pharmaceutical Company Limited as a process chemist and has had numerous projects for the manufacturing of drug candidates. Based on his research results during his 16-year career, he obtained his Ph.D. in 2007 under Professor Hironao Sajiki from Gifu Pharmaceutical University. He has been listed in MARQUIS Who's Who in the World and will be listed in IBC 2000 Outstanding Intellectuals of the 21st Century.



Mitsuhisa Yamano was born in 1961 in Osaka, Japan. After undergraduate studies at Kyoto University in 1983, he obtained his M.Sc. degree in engineering at Kyoto University in 1985. Since 1985, he has worked at Takeda Pharmaceutical Company Limited as a researcher on process development for new drug candidates. He spent 1 year in the group of Professor Barry M. Trost at Stanford University as a visiting scholar from 1999 until 2000. His research interests include process chemistry, especially asymmetric synthesis.

Jun Takeuchi was born in Kyoto, Japan, in 1967 and received his B.S. in 1991 and M.S. in 1993 from Osaka University. He received his Ph.D. in 1996 under the direction of Professor Chuzo Iwata from Osaka University. He has been working at ONO Pharmaceutical Co., Ltd. since 1996. In 2006, he began his visiting scholar studies at the University of California, Berkeley in the laboratories of Professor Jonathan A. Ellman. His research interest is in the area of medicinal chemistry.

ONE-FLASK SYNTHESIS OF METHYL ARYLVINYLDIAZOACETATES AND THEIR APPLICATION IN ENANTIOSELECTIVE C–H FUNCTIONALIZATION: SYNTHESIS OF (*E*)-METHYL 2-DIAZO-4-PHENYLBUT-3-ENOATE AND (*S,E*)-METHYL 2-((*R*)-4-METHYL-1,2-DIHYDRONAPHTHALEN-2-YL)-4-PHENYLBUT-3-ENOATE



Submitted by James R. Manning and Huw M. L. Davies.[1]
Checked by Scott E. Denmark and William R. Collins.

1. Procedure

A. *2-Carboxyethyltriphenylphosphonium chloride.* 3-Chloropropionic acid (16.3 g, 150 mmol) (Note 1) and triphenylphosphine (43.3 g, 165 mmol, 1.1 equiv) (Note 2) are added to a 250-mL, round-bottomed flask equipped with a magnetic stir bar. Xylenes (75 mL) (Note 3) are added and a water-cooled condenser is attached to the flask. Vigorous stirring is commenced and the solution is heated to reflux in an oil bath for 3 h during which time two layers form. The flask is then removed from the oil bath and the flask is fitted with a thermometer. When the solution has cooled to 60–70 °C, the

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thermometer is removed and acetonitrile (50 mL) (Note 4) is slowly added with vigorous stirring and scraping using a metal spatula to prevent the product from sticking to the sides of the flask (Note 5). The product, which is eventually converted to a white solid, is collected by vacuum filtration in a Büchner funnel. The product is washed with diethyl ether (300 mL) (Note 6) and then dried under vacuum (0.05 mmHg) for 2 h to afford 46.6–46.7g (84%) of pure 2-carboxyethyltriphenylphosphonium chloride as a white solid (Note 7).

B. *1-Methyl-3,4-dihydronaphthalene.* A 500-mL, 3-necked round-bottomed flask equipped with a stir bar is fitted with an argon inlet adaptor, a 100-mL pressure-equalized addition funnel and a reflux condenser. The tops of the addition funnel and reflux condenser are sealed with septa, the apparatus is flame dried under vacuum (0.05 mmHg) and then is backfilled with argon. Magnesium turnings (3.65 g, 150 mmol, 1.50 equiv) (Note 8) are then added and the flask is evacuated and filled with argon twice. Dry diethyl ether (100 mL) (Note 9) is added through the condenser via cannula. Iodomethane (9.98 mL, 22.7 g, 160 mmol, 1.60 equiv) (Note 10) is then added by syringe to the addition funnel. Stirring is commenced and the iodomethane is added dropwise to the magnesium turnings at a rate sufficient to maintain a gentle reflux (13–17 min is required to complete the addition). The solution is then stirred for another 20 min after the addition is complete. A solution of α-tetralone (14.6 g, 100 mmol) (Note 11) in dry diethyl ether (10 mL) is transferred via syringe from a flame-dried 100-mL round bottom flask to the addition funnel and then added dropwise to the methyl magnesium iodide solution at a rate sufficient to maintain a gentle reflux (12–16 min is required for the addition). The solution is stirred for another 15 min after completion of the addition. The rubber septa are then removed from the tops of both the condenser and the addition funnel. An aqueous solution of 3 N HCl (60 mL) is placed in the addition funnel and then is added dropwise to the solution over 30 min. The mixture is then vigorously stirred for 1 h at room temperature, after which time the mixture is poured into a 250-mL separatory funnel and the layers are separated. The aqueous layer is extracted with diethyl ether (3 x 30 mL). The combined ether extracts are washed with brine (50 mL), dried over anhydrous $MgSO_4$, vacuum filtered through a plug of silica gel (24 g) in a Büchner funnel and then concentrated by rotary evaporation at room temperature. The residue is purified by flash column chromatography on 130 g of silica gel (Note 12) eluting with pentane (450 mL). The fractions containing product are collected and concentrated by rotary evaporation (11 mmHg, room temperature) to afford 13.1–13.2 g (91–92%) of pure 1-methyl-3,4-dihydronaphthalene as a clear oil (Notes 13, 14).

C. *(E)-Methyl 2-diazo-4-phenylbut-3-enoate.* 2-Carboxyethyl-triphenylphosphonium chloride (26.7 g, 72.0 mmol, 1.20 equiv) is added to a flame-dried, 2-necked 500-mL, round-bottomed flask equipped with a magnetic stir bar and fitted with a rubber septum and an argon inlet adaptor. The flask is evacuated (0.05 mmHg) and filled with argon two times after which a positive argon pressure is maintained on the flask. Benzaldehyde (6.07 mL, 6.37 g, 60.0 mmol) (Note 15) and THF (130 mL) (Note 16) are then added by syringe and the flask is externally cooled to 0 °C in an ice-water bath and vigorous stirring is begun. A solution of potassium *tert*-butoxide (16.8 g, 150 mmol, 2.5 equiv) in THF (80 mL) under an argon atmosphere and at 0 °C is then added *via* cannula under positive argon pressure over 30 min (Notes 16, 17). After the addition is complete, the solution is stirred at 0 °C for 30 min, then the ice-water bath is removed and stirring is continued for another 20 min. Dimethyl sulfate (11.4 mL, 15.1 g, 120 mmol, 2.0 equiv) (Note 18) is then added rapidly by syringe and stirring is continued at ambient temperature for 2.5 h. The septum is then briefly removed from the flask and *para*-acetamidobenzenesulfonyl azide (18.7 g, 78.0 mmol, 1.30 equiv) (Note 19) is added in one portion. The septum is replaced and the flask, under a positive argon pressure, is externally cooled to 0 °C in an ice-water bath. DBU (11.7 mL, 11.9 g, 78.0 mmol) (Note 20) is then added rapidly by syringe and the solution quickly becomes red. Stirring is continued at 0 °C for 4 h and then the solution is allowed to warm to room temperature and then is transferred to a 1-L, single-necked, round-bottomed flask and the solution is concentrated by rotary evaporation (27 mmHg, ambient temperature) (Note 21). The residue is treated with saturated aqueous ammonium chloride solution (150 mL) and diethyl ether (400 mL) and the mixture is poured into a 1-L separatory funnel and vigorously shaken. The aqueous layer is drained and the organic layer is washed with saturated ammonium chloride solution (150 mL) and then is dried over anhydrous $MgSO_4$ (5 g) (Note 22). The solvent is removed by rotary evaporation (11 mmHg, room temperature) to give a dark-red oil. The oil is then adsorbed onto 50 g of silica gel, which is then placed at the top of a packed column of silica gel (350 g) (Note 23). The column is eluted with pentanes/diethyl ether, 12:1. The red fractions containing the product are collected and concentrated by rotary evaporation at room temperature to afford 9.3–9.7 g (77–80%) of **1** as a red solid (Note 24).

D. *(S,E)-Methyl 2-((R)-4-methyl-1,2-dihydronaphthalen-2-yl)-4-phenylbut-3-enoate.* 1-Methyl-3,4-dihydronaphthalene (5.34 g, 37.0 mmol) and Rh_2(*S*-DOSP)$_4$ (7.0 mg, 0.0037 mmol, 0.0001 equiv) (Note 25) are added to a flame-dried, 250-mL 2-necked, round-bottomed flask equipped with a magnetic stir bar and fitted with an argon inlet adaptor and a rubber septum. The flask is evacuated (0.05 mmHg) and purged with argon twice and then maintained under a positive argon pressure. 2,2-Dimethylbutane (40 mL) (Note 26) is added by syringe and vigorous stirring is begun. A solution of (*E*)-methyl 2-diazo-4-phenylbut-3-enoate **1** (8.23 g, 40.7 mmol, 1.10 equiv) (Note 27) in 2,2-dimethylbutane (60 mL) is added by syringe pump over 4 h (Note 28). The solution is stirred for an additional 10 h and the solvent is then removed by rotary evaporation (11 mmHg, room temperature) to give a light-yellow solid. Absolute ethanol (20 mL) is added to the crude material and a reflux condenser is attached to the flask. The solution is heated to reflux to dissolve the material and then allowed to cool to room temperature, whereupon the product crystallizes as an off-white solid. The solution is then cooled to 0 °C for 2 h and the product is collected by vacuum filtration on a Büchner funnel to give 8.0–8.3 g (68–70%) of pure **2** as an off-white solid (Note 29).

2. Notes

1. 3-Chloropropionic acid was purchased from Acros Organics and used as received.
2. Triphenylphosphine was purchased from Acros Organics and used as received.
3. Xylenes were purchased from Mallinckrodt Inc. and used as received.
4. Acetonitrile was purchased from J. T. Baker and used as received.
5. Scraping the precipitated material was crucial to induce solidification of the product, which initially separated out of the xylene solution as a taffy-like material.
6. Washing should be continued with diethyl ether until the wash solvent no longer appears white after filtration.
7. The product displayed the following properties: mp 201–204 °C (sealed tube); IR (neat): cm^{-1} 2900, 1742, 1421, 1586, 1489, 1439, 1421, 1388, 1352, 1220, 1165, 1116, 1037, 996, 950, 910, 859, 816, 752, 698, 613; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.09–3.15 (m, 2 H), 3.69–3.75 (m, 2 H),

7.69–7.84 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1, 28.1, 117.2, 130.4, 133.4, 171.3, 135.2; LRMS EI (relative intensity) *m/z*: 369 ($[M]^+$, 6), 317 (5), 262 (100), 183 (25), 152 (4); Anal. Calcd for $C_{21}H_{20}ClO_2P$: C, 68.02; H, 5.44. Found: C, 68.03; H, 5.48. The spectroscopic data were consistent with previously reported literature values.[2a,b] The procedure described herein is a modified version of a literature procedure.[2b]

8. Magnesium turnings were purchased from Fisher Scientific and used as received.

9. Diethyl ether was purchased from EMD Chemicals Inc., dried over 4Å molecular sieves overnight and further dried by pressure filtration through activated alumina.

10. Iodomethane (99%) was purchased from Aldrich Chemical Company, Inc. and used as received. It is classified as a carcinogen and should be handled with care

11. α-Tetralone was purchased from Aldrich Chemical Company, Inc. (98%) and used as received.

12. Silica gel was purchased from Silicycle (40-63 μm particle size, 60 Å pore diameter) and loaded as a slurry onto a 30-mm diameter column. Fractions were collected (19 mL) and elution monitored by TLC (silica gel, R_f 0.51, pentane).

13. The submitters occasionally found that the product was contaminated with the isomeric 1-methylene-1,2,3,4-tetrahydronaphthalene in a 25:1 ratio on some of the trials. This impurity was inseparable by chromatography but was converted quantitatively to the desired product by refluxing the mixture in toluene with 1 mol % toluenesulfonic acid monohydrate for 1 h.

14. The product displayed the following properties: R_f 0.51 (pentanes); IR (neat): cm^{-1} 3097, 3060, 2933, 2883, 2830, 2856, 1487, 1450, 1438, 1427, 1378, 1239, 1069, 1039, 1020, 936, 886, 868, 812, 791, 756, 731, 704, 633; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.09 (s, 3 H), 2.27–2.31 (m, 2 H), 2.79 (t, *J*=8.5 Hz, 2 H), 5.88 (m, 1 H), 7.17–7.22 (m, 2 H), 7.22–7.29 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 28.6, 122.9, 125.6, 126.5, 126.9, 127.6, 132.4, 136.1, 136.5; LRMS EI (relative intensity) *m/z*: 144 ($[M]^+$, 100), 129 (47), 115 (10), 102 (4), 89 (5), 77 (3), 63 (5); Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.57; H, 8.22. The spectroscopic data were consistent with previously reported literature values.[3] The procedure described herein is a modified version of a literature procedure.[3]

15. Benzaldehyde (redistilled, 99.5+%) was purchased from Aldrich Chemical Company, Inc. and used as received.

16. THF was purchased from J. T. Baker Chemical Co., dried over 4 Å molecular sieves overnight and further dried by pressure filtration through activated alumina.

17. Potassium *tert*-butoxide (98+%) was purchased from Acros Organics and used as received. The solution in THF was cooled externally to 0 °C in an ice-water bath before and during addition.

18. Dimethyl sulfate was purchased from Acros Organics and used as received. It is classified as a carcinogen and should be handled with care.

19. *p*-Acetamidobenzenesulfonyl azide (*p*-ABSA) is commercially available (Aldrich Chemical Company, Inc.), but was prepared by the submitters using the published procedure, See *Org. Synth., Coll. Vol. IX* **1998**, 422. Although the compound has not exhibited shock sensitivity,[4] *all azide compounds should be handled with care.*

20. DBU was purchased from Acros Organics and used as received.

21. The reaction mixture was concentrated on a rotary evaporator in a fume hood because of the excess dimethyl sulfate that was collected in the receiver.

22. Anhydrous $MgSO_4$ was purchased from Fisher Scientific Company.

23. Silica gel was purchased from Silicycle (40–63 μm particle size, 60 Å pore diameter) and loaded as a slurry onto a 60-mm diameter column.

24. The product displayed the following properties: R_f 0.35 (9:1 pentane/ether); IR (neat): cm^{-1} 2960, 2168, 2088($C=N_2$), 1706, 1626, 1492, 1449, 1438, 1405, 1364, 1318, 1286, 1243, 1194, 1113, 1010, 950, 752, 734, 692; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3 H), 6.20 (d, *J* =16.0 Hz, 1 H), 6.49 (d, *J*= 16.0 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.30–7.37 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.05, 111.0, 122.8, 125.6, 126.8, 128.4, 136.5, 165.0; LRMS EI (relative intensity) *m/z*: 202.1 ($[M]^+$, 38), 170.0 (10), 159 (4), 142 (12), 129 (16)); Anal. Calcd for $C_{11}H_{10}N_2O_2$ C, 65.34; H, 4.98; N, 13.85, Found: C, 65.40; H, 4.94; N, 13.70 The procedure described herein is a modified version of a literature procedure.[5] The product should be stored at 0 °C and immediately purified before use if stored for more than ~2 days as it will slowly undergo an electrocyclization reaction to form a pyrazole. The pyrazole is observed as a white crystalline solid. *All diazo compounds should be handled carefully,* although in this case, the only thermal decomposition pathway exhibited by this compound in the absence of catalyst is electrocyclization to the pyrazole. The compound should not be stored in solution as this accelerates the decomposition reaction.

25. Rh_2(*S*-DOSP)$_4$ is commercially available from Strem Chemicals, Inc. and Aldrich Chemical Company, Inc. and is air stable. Alternatively, it can be readily made by the published procedure.[6]

26. 2,2-Dimethylbutane (DMB) was purchased from Lancaster Synthesis and distilled from sodium under argon prior to use.

27. (*E*)-Methyl 2-diazo-4-phenyl-3-butenoate **1** was freshly purified when used. The checkers found that 500 μL of diethyl ether was needed to wet the solid before it was diluted with DMB. If the diethyl ether was not used, the starting material was not completely soluble in the DMB.

28. The checkers found that carrying out the syringe pump addition with a 50-mL syringe led to clogging from formation of the insoluble pyrazole. The best results were obtained by carrying out the addition in six portions with a 10-mL syringe with a 16-gauge needle (40 min per addition for the total of a 4-h addition period).

29. The product was obtained in 87–92% yield when purified by silica gel column chromatography (See Table 2), but contained a slight greenish tinge. The product displayed the following properties: mp 77–79 °C (sealed tube), R_f 0.35 (10:1 pentane/ether); IR (KBr): cm^{-1} 2946, 1956, 1886, 1735, 1638, 1487, 1450, 1427, 1380, 1331, 1298, 1264, 1215, 1151, 1098, 1024, 993, 972, 944, 902, 842, 807, 761, 723, 659; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.07 (s, 3 H), 2.72 (m, 1 H), 2.84–2.88 (m, 2 H), 3.11 (t, *J*=9.5 Hz, 1 H), 3.69 (s, 3 H), 5.73 (d, *J*=3.5 Hz, 1 H), 6.14 (dd, *J*=16.0, 9.5 Hz, 1 H), 6.42 (d, *J*=16.0 Hz, 1 H), 7.08 (d, *J*= 7.0 Hz, 1 H), 7.15 (td, *J*= 7.0, 2.0 Hz, 1 H), 7.23–7.24 (m, 4 H), 7.30–7.36 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.4 (CH_3), 31.7, 36.1, 51.9, 53.2, 123.0, 126.0, 126.2, 126.4, 126.6, 127.2, 127.7, 127.8, 128.5, 134.4, 135.3, 136.6, 173.6; LRMS ESI (relative intensity) *m/z*: 319.2 ($[M+H]^+$,7), 341.1 ($[M+Na]^+$, 0.4), 287 (3), 259.1 (3), 176 (100), 143 (94); HPLC analysis: >99.8:0.2 (unable to accurately integrate minor enantiomer) (Chiralcel OD-H, 2% *i*-PrOH in hexane, 0.8 mL/min, λ = 254 nm, t_R = 7.25 min , major; t_R = 7.99 min, minor); Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.62; H, 6.94. $[\alpha]_D$ = –21.4 (c = 1.0, ethanol). The procedure described herein is a modified version of a literature procedure.[7]

Safety and Waste Disposal Information

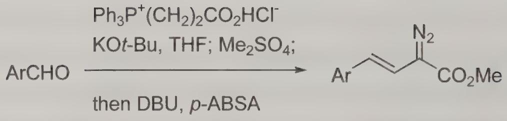
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

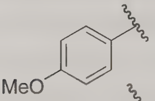
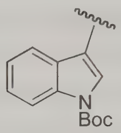
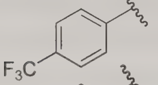
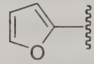
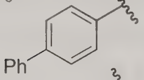
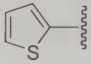
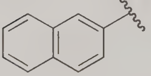
3. Discussion

Dirhodium tetracarboxylate based catalysts efficiently decompose diazo compounds to generate reactive metal carbenoids that are capable of undergoing extraordinarily regio- and stereoselective reactions.[8] This is especially true when such catalysts are used in conjunction with diazo compounds that contain both electron-donating groups (EDG) and electron-withdrawing groups (EWG). Our work over the last decade in this area has shown that the prolinate based catalyst $Rh_2(S\text{-DOSP})_4$ and its second generation relative, the bridged catalyst $Rh_2(S\text{-biTISP})_2$ can routinely produce highly diastereo- and enantioselective intermolecular cyclopropanation reactions with the latter catalyst capable of achieving very high turnover numbers (92,000).[9]

While highly stereoselective cyclopropanation reactions have been known for some time, asymmetric intermolecular C–H activation reactions are a more recent development. Extensive work in this area in recent years has led to carbenoid surrogates for many classic organic transformations including the aldol addition,[10] the Mannich reaction,[11] and the Claisen rearrangement.[12] $Rh_2(S\text{-DOSP})_4$ has been an exceptional catalyst for these transformations and has been found to perform best with diazo compounds substituted with both a methyl ester (EWG) and an aryl, heteroaryl, or vinyl group (EDG). C–H activation products are regularly formed as single diastereomers and with >90% ee. One of the more spectacular transformations discovered in recent years using this catalyst has been the combined C–H activation/Cope rearrangement reaction.[7,13] It occurs when a vinyl-substituted carbenoid undergoes a C–H activation of an allylic C–H bond that is interrupted by a Cope rearrangement. The product of this transformation will then normally undergo a retro-Cope rearrangement at room temperature or upon heating in toluene to give the thermodynamically more stable "formal" C–H activation product. This transformation is extremely efficient with dihydronaphthalenes as substrates and routinely produces products in high yields and with >98% ee. The process is amenable to a variety of vinyldiazoacetates and substituted dihydronaphthalenes. The procedure described here can be used to synthesize many different vinyldiazoacetates starting from readily available aromatic aldehydes. Several examples of this are shown in Table 1,[5] performed on a 5-mmol scale.

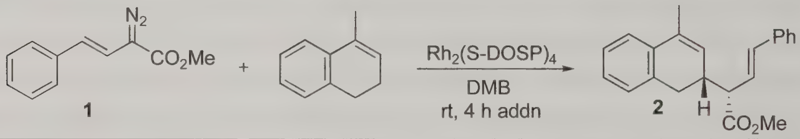
Table 1.



Ar	Yield (%)	Ar	Yield (%)
	65		49
	46		69
	49		62
	55		

The combined C–H activation/Cope rearrangement reaction has proven to be a very favorable transformation and catalyst loadings as low as 0.01 mol% can be used with no significant drop in yield or stereoselectivity (Table 2).

Table 2.



diazo (mmole)	substrate (mmole)	catalyst (mole %)	catalyst T.O.	yield[a] (%)	de (%)	ee (%)
1.20	1.00	0.10	920	92	>94	99.3
12.0	10.0	0.050	1740	87	>94	99.4
12.0	10.0	0.040	2300	92	>94	99.5
12.0	10.0	0.030	2967	89	>94	99.7
12.0	10.0	0.020	4550	91	>94	99.2
12.0	10.0	0.010	9100	91[b]	>94	99.5
12.0	10.0	0.0075	-	73[c]	>94	97.3

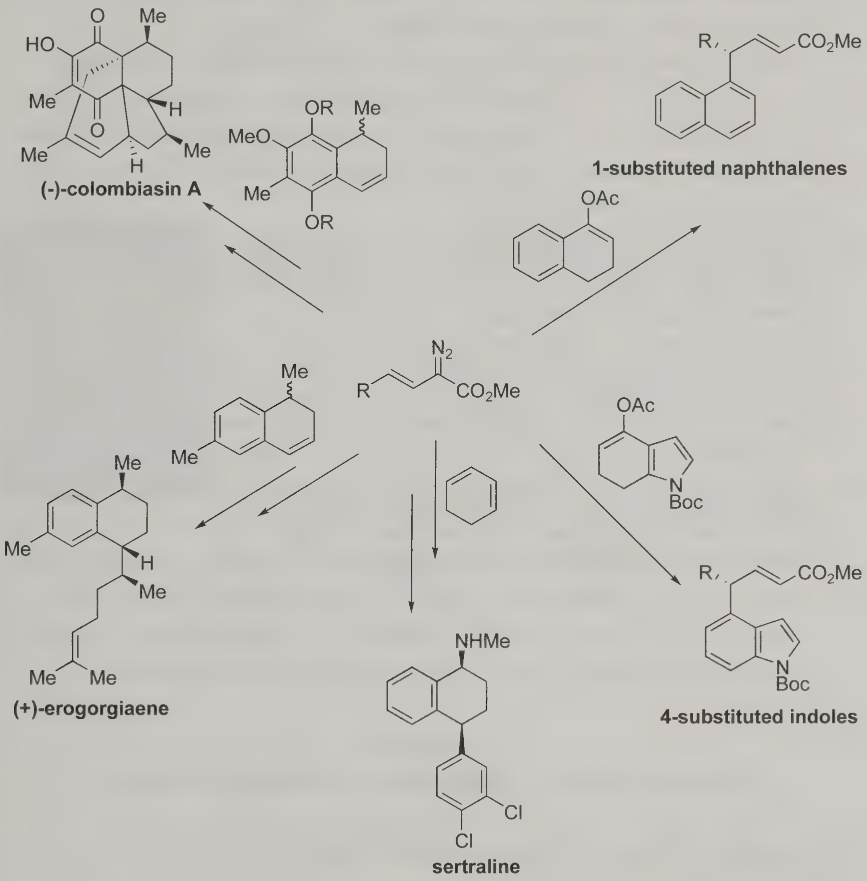
[a] isolated yield after flash column chromatography

[b] solution was green at the end of addition-TOF at least 2275 h^{-1}

[c] reaction incomplete-yield from crude ^1H NMR ratio of product:sm (2.7:1)

The procedure described here is readily performed on a large scale, as the amount of catalyst required is small compared to the product generated and the crude reaction mixture is easily recrystallized from ethanol to give the pure product, requiring no other purification steps. Although the sequence is illustrated with a methyl-substituted dihydronaphthalene, unsubstituted substrates and other substituents, including siloxy and acetoxy, can be used.[7] This methodology has been successfully used in a variety of applications, including total synthesis (Scheme 1).[7,13]

Scheme 1.



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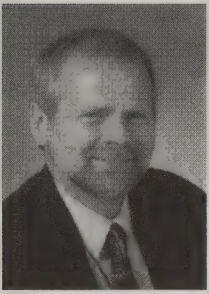
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

3-Chloropropionic acid: Propanoic acid, 3-chloro-; (107-94-8)
Triphenylphosphine; (603-35-0)
2-Carboxyethyltriphenylphosphonium chloride; (36626-29-6)
Iodomethane; (74-88-4)
Magnesium (7439-95-4)

α-Tetralone: 1(2H)-Naphthalenone, 3,4-dihydro-; (529-34-0)
1-Methyl-3,4-dihydronaphthalene: Naphthalene, 1,2-dihydro-4-methyl-; (4373-13-1)
(*E*)-Methyl 2-diazo-4-phenylbut-3-enoate: (119987-21-2)
Benzaldehyde; (100-52-7)
Potassium *tert*-butoxide: 2-Propanol, 2-methyl-, potassium salt (1:1); (865-47-4)
Dimethyl sulfate: Sulfuric acid, dimethyl ester; (77-78-1)
p-Acetamidobenzenesulfonyl azide: Benzenesulfonyl azide, 4-(acetylamino)-; (2158-14-7)
DBU: Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro-; (6674-22-2)
(*S,E*)-Methyl 2-((*R*)-4-methyl-1,2-dihydronaphthalen-2-yl)-4-phenylbut-3-enoate: 2-Naphthaleneacetic acid, 1,2-dihydro-4-methyl-α-[(1E)-2-phenylethenyl]-, methyl ester, (αS,2R)-; (76531-50-5)
Rh_2(*S*-DOSP)$_4$; (179162-34-6)

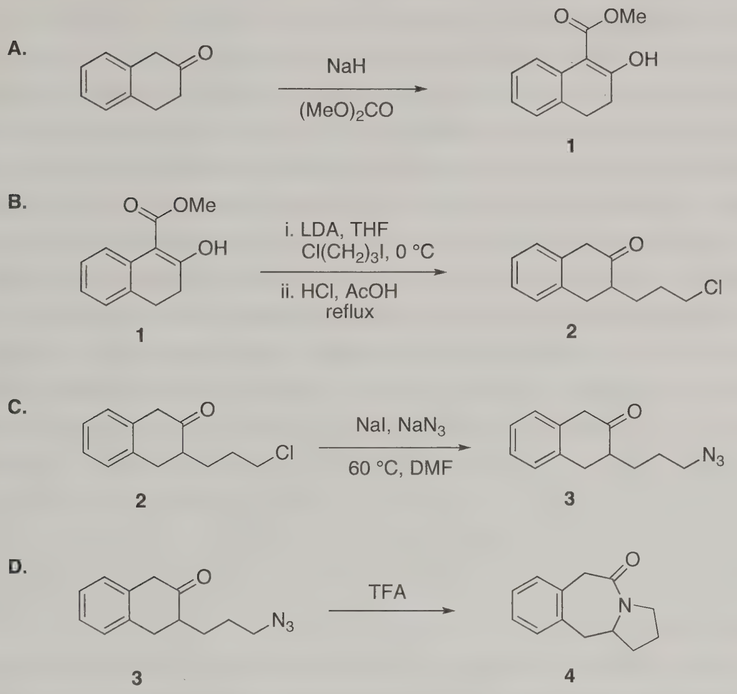


Huw M. L. Davies was born in Aberystwyth, Wales, UK. He received his B.Sc. from University College Cardiff, Wales and his Ph.D. from the University of East Anglia, England. After a post-doctoral position at Princeton University, he joined the faculty at Wake Forest University. In 1995 he moved to the University at Buffalo, the State University of New York, where he currently holds the position of UB Distinguished Professor and Larkin Professor of Organic Chemistry. His research program covers design of chiral catalysts, development of new synthetic methodology, total synthesis of biologically active natural products, and development of chiral therapeutic agents. A major current theme is catalytic asymmetric C–H functionalization by means of rhodium-carbenoid induced C–H insertion.

James R. Manning was born in 1979 in Swanton, Vermont. He received his B.S. degree in chemistry (2002) from the University of Vermont while performing undergraduate research in the laboratory of Professor Gregory K. Friestad. He is currently a doctoral student at the University at Buffalo, The State University of New York under the guidance of Professor Huw M. L. Davies. His research is focused on the exploration of rhodium-catalyzed intermolecular carbenoid reactions in the context of methodology development for the synthesis of pharmaceutically relevant compounds and natural product synthesis. Mr. Manning is the recipient of an NIH predoctoral fellowship.

William R. Collins' interest in organic chemistry began at the New Mexico Institute of Technology during an undergraduate project under Dr. Michael Heagy which involved the design and synthesis of boronic acid chemosensors for carbohydrate recognition. After a National Science Fellowship Undergraduate Research Experience (NSF REU) in 2001 at the University of New Mexico with Dr. Patrick Mariano studying photochemically induced macrocyclizations of phthalimides, he became more interested in synthesis and methodology. His current project focuses on expansion of the scope of the Lewis base catalyzed asymmetric variant of the Passerini reaction.

SYNTHESIS OF AN *N*-SUBSTITUTED LACTAM USING AN INTRAMOLECULAR SCHMIDT REACTION: FORMATION OF 2,3,11,11a-TETRAHYDRO-1*H*-BENZO[d]PYRROLO[1,2-a]AZEPIN-5(6*H*)-ONE



Submitted by Scott Grecian and Jeff Aubé.
Checked by Dalian Zhao and David J. Mathre.

Caution! *Sodium azide is toxic as well as heat and shock sensitive. Metallic and sharp surfaces should be avoided.*

1. Procedure

A. Methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**1**). An oven-dried 250-mL three-necked, round-bottomed flask equipped with a glass stopper, thermometer, rubber septum, large magnetic stirring bar, and two venting needles is charged with 8.0 g (200 mmol) of 60% sodium hydride in mineral oil by temporarily removing the glass stopper. The suspension is then washed with three 30 mL portions of anhydrous hexanes using a syringe through the septum. Anhydrous dimethyl carbonate is added (Note 1) (120 mL) and the mixture is cooled to 5 °C with an ice bath. β-Tetralone (Note 2) (13.3 mL, 100 mmol) is added via syringe over 20 min. The resulting green/brown mixture is then stirred for 1 h, at which time the ice bath is removed and the reaction is warmed to 23 °C. After 12 h, the glass stopper is removed and the reaction flask is fitted with a reflux condenser and heated to reflux for 1 h in an oil bath (Note 3). The brown mixture is cooled to room temperature, the condenser is removed, 20 mL of water is added dropwise and the mixture is poured into a 1-L separatory funnel followed by the addition of 200 g of ice and the slow addition of 250 mL of 1.0 M HCl. The mixture is extracted with diethyl ether (3 x 100 mL). The ethereal extracts are combined and washed once with 150 mL of brine and dried with magnesium sulfate, filtered and concentrated to give 20–25 g of a red oil. The oil is transferred to a 100-mL round-bottomed flask and topped with a short path distillation head fitted with a thermometer and four receiving flasks submerged in an ice bath. Vacuum distillation is performed at 0.9 mm Hg while the oil bath temperature is increased gradually to 185 °C. The first several drops are collected between 136 and 141 °C and discarded. Methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**1**) is collected between 138 and 141 °C as a pale yellow oil (16.9 – 17.8 g, 83–87%) (Notes 4 and 5).

B. 3-(3'-Chloropropyl)-3,4-dihydronaphthalen-2(1H)-one (**2**). To an oven-dried 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, a thermometer, a glass stopper, and a magnetic stir bar is added 120 mL of freshly distilled THF and diisopropylamine (15.1 mL, 108 mmol) (Note 6) by syringe through the septum. After cooling the flask to 0 °C in an ice bath, 45 mL of *n*-butyllithium (105 mmol, 2.32 *M* /hexanes) are added dropwise over 10 min while maintaining the temperature at or below 10 °C (Note 7). After an additional 45 min, methyl 2-hydroxy-3,4-dihydronaphthalene-1-carboxylate (**1**) (10.0 g, 49 mmol) dissolved in 25 mL of THF is added via cannula through the syringe over 15 min while maintaining the reaction temperature below 10 °C (Note 8). After 15 min, the ice bath is removed and the reaction is stirred for 1 h at which time it is cooled to 0 °C in an ice bath. After an additional 30 min, 1-chloro-3-iodopropane (6.22 mL, 59 mmol) (Note 9) is added in several portions via syringe over 25 min while maintaining the reaction temperature below 10 °C. The ice bath is removed after 30 min, and the reaction is stirred for an additional h, at which time the reaction is quenched by the slow addition of 50 g of ice. The mixture is transferred to a separatory funnel and 150 mL of 1.0 M HCl is added slowly. The organic layer is separated and the mixture is extracted with diethyl ether (2 x 100 mL). The combined organic layers are washed once with 175 mL of brine, dried with magnesium sulfate, filtered and concentrated to give a red oil (15.2–15.8 g) (Note 10). The oil is transferred to a 100-mL, single-necked, round-bottomed flask equipped with a stir bar and a reflux condenser, and the oil is dissolved in 35 mL of glacial acetic acid. Concentrated HCl (5 mL) is added. The mixture is stirred at room temperature for 30 min, then placed in an oil bath and heated to 110 °C for 3 h, then cooled to room temperature and poured into a separatory funnel followed by the addition of 100 mL of water and 75 mL of diethyl ether. The aqueous layer is extracted with diethyl ether (2 x 75 mL). The combined extracts are washed with a saturated solution of sodium bicarbonate (3 x 100 mL) (Note 11). The organic layer is then washed once with 150 mL of brine, dried over magnesium sulfate, filtered and concentrated to a red oil (11.7–12.0 g). The oil is chromatographed over 100 g of silica gel (25 × 5 cm) starting with 500 mL of 5% ethyl acetate/hexanes followed by 500 mL of 10% ethyl acetate/hexanes. The desired product is collected in fractions 28 to 40 (25 mL fractions), which upon concentration, gives 8.1–8.2 g (73–74% from **1**) of 3-(3′-chloropropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**2**) as a light yellow oil (Note 12).

C. 3-(3′-Azidopropyl)-3,4-dihydronaphthalen-2(1H)-one (**3**). In a 100-mL single-necked round-bottomed flask equipped with a stir bar is dissolved 3-(3-chloropropyl)-3,4-dihydronaphthalen-2(1H)-one (**2**) (5.0 g, 22 mmol) in 60 mL of anhydrous *N,N*-dimethylformamide. A blasting shield is placed around the reaction flask and sodium iodide (3.96 g, 26.4 mmol) (Note 13) and sodium azide (2.86 g, 44.0 mmol) (Note 14) are added. The mixture is stirred while immersed in an oil bath heated to 60 °C for 12 h, after which time the reaction mixture is poured into 150 mL of water and extracted with diethyl ether (2 x 100 mL) (Notes 15 and 16). The organic layer is washed with brine (3 x 150 mL), dried with magnesium sulfate, filtered and concentrated at or below 30 °C to a red oil (4.9–5.2 g). The oil is loaded on a column of 60 g of silica gel (18 × 5 cm) and eluted with 750 mL of 10% ethyl acetate/hexanes. The desired product is collected in fractions 18-28 (25 mL fractions) which, after concentration, gives 4.10–4.24 g (81–84%) of 3-(3′-azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one (**3**) as a red oil (Note 17).

D. 2,3,11,11a-Tetrahydro-1H-benzo[d]pyrrolo[1,2-a]azepin-5(6H)-one (**4**). An oven-dried, three-necked 100-mL round-bottomed flask is equipped with a thermometer, rubber septum, an elbow adapter connected to a tygon tube with an in-line bubbler, and a stir bar. 3-(3′-Azidopropyl)-3,4-dihydronaphthalen-2(1H)-one (4.0 g, 17.44 mmol) of (**3**) is added to the flask by temporarily removing the septum and cooled to 0 °C in an ice-bath. Trifluoroacetic acid (Note 18) (20 mL) is added dropwise through the septum by syringe over 15 min (Note 19). After 30 min, the ice bath is removed and the reaction is allowed to ~~warms~~ to room temperature. After an additional 30 min, 50 mL of water is added to the reaction, which is then poured into a separatory funnel. The aqueous layer is extracted with chloroform (3 x 40 mL). The organic extracts are combined and washed with 100 mL of a saturated solution of sodium bicarbonate, dried with magnesium sulfate, filtered and concentrated to an orange solid (3.7–4.0 g). The solid is dissolved in 5 mL of hot chloroform, loaded onto a column of 40 g of silica gel (10 × 5 cm) and eluted with 350 mL of 20% ethyl acetate/hexanes followed by 500 mL of ethyl acetate. The desired product is collected in fractions 19-34 (25 mL fractions) which, after concentration, gives 2.87–3.09 g (82–88%) of 2,3,11,11a-tetrahydro-1H-benzo[d]-pyrrolo[1,2-a]azepin-5(6*H*)-one (**4**) as an off-white solid (Note 20).

2. Notes

1. Sodium hydride and dimethyl carbonate were purchased from Aldrich Chemical Company, Inc.

2. 3,4-Dihydronaphthalen-2(1*H*)-one (β-tetralone) was purchased from Aldrich Chemical Company, Inc.

3. The reaction progress was monitored by silica gel thin layer chromatography.

4. This compound was prepared according to the procedure described in Oommen, P. K. *Aust. J. Chem*. **1976**, *29*, 1393-1396.

5. The product exhibited the following properties: $R_f = 0.48$ (1:9, ethyl acetate/hexanes); IR (neat): 1640, 1595, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.59 (t, *J* = 7.3 Hz, 2 H), 2.86 (t, *J* = 7.3 Hz, 2 H), 3.96 (s, 3 H), 7.18–7.12 (m, 2 H), 7.25 (t, *J* = 10.2 Hz, 1 H), 7.75 (d, *J* = 6.7 Hz, 1 H), 13.39 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.8, 29.6, 51.8, 99.9, 125.0, 125.9, 126.5, 127.3, 131.4, 133.2, 172.5, 178.5; MS (FAB) *m/z* (relative intensity): 204 (M^+, 99), 172 (100); HRMS calcd for $C_{12}H_{13}O_3$ (MH^+): 205.0865, found: 205.0853.

6. Anhydrous diisopropylamine was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

7. *n*-Butyllithium was purchased from the Aldrich Chemical Company, Inc., and titrated prior to use. For the titration procedure used, see: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879-1880.

8. A voluminous light yellow precipitate began to form near the end of the addition.

9. 1-Chloro-3-iodopropane was purchased from Aldrich Chemical Company, Inc.

10. An aliquot (285 mg) was loaded on 10 g of silica gel and eluted with 5% ethyl acetate/hexanes. Concentration of the fractions containing the product gave 178 mg of methyl 3-(3-chloropropyl)-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate as a light yellow oil. This product exhibited the following physical properties: R_f = 0.40 (1:9, ethyl acetate/hexanes); IR (neat): 3440, 1735, 1640, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.51–1.57 (m, 1 H), 1.67–1.71 (m, 1 H), 1.84–1.93 (m, 2 H), 2.55–2.59 (m, 1 H), 2.66 (dd, *J* = 4.9, 15.1 Hz, 1 H), 3.06 (dd, *J* = 5.6, 15.1 Hz, 1 H), 3.53 (sextet, *J* = 6.9 Hz, 2 H), 3.95 (s, 3 H), 7.09–7.16 (m, 2 H), 7.22 (dt, *J* = 1.5, 7.1 Hz, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 13.49 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.0, 30.3, 33.2, 38.5, 44.7, 51.9, 99.3, 125.2, 125.8, 126.5, 128.0, 130.6, 131.5, 172.7, 180.4; MS (FAB) *m/z* (relative intensity): 280 (M^+, 100), 248 (77); HRMS calcd for $C_{15}H_{17}ClO_3$ (M^+): 280.0866, found: 280.0873.

11. Significant gas evolution was observed upon addition of a saturated solution of sodium bicarbonate.

12. The product exhibited the following properties: R_f = 0.41 (1:4, ethyl acetate/hexanes); IR (neat): 2955, 1710, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.58–1.62 (m, 1 H), 1.87–1.97 (m, 3 H), 2.48 (sextet, *J* = 6.4 Hz, 1 H), 2.89 (dd, *J* =10.3 Hz, 15.4, 1 H), 3.13 (dd, *J* = 5.5 Hz, 15.4, 1 H), 3.58 (sextet, *J* = 4.4 Hz, 2 H), 3.62 (d, *J* = 8.1 Hz, 2 H), 7.14 (m, 1 H), 7.24 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.1, 30.1, 34.4, 44.4, 44.8, 46.7, 126.8, 126.9, 127.8, 128.0, 133.1, 135.6, 210.9; MS (FAB) *m/z* (relative intensity): 223 (MH^+, 100); HRMS calcd for $C_{13}H_{16}ClO$ (MH^+): 223.0890, found: 223.0890.

13. Sodium iodide and sodium azide were purchased from the Aldrich Chemical Company Inc.

14. **Caution**: *Sodium azide is explosive and toxic. Metallic and sharp surfaces should be avoided.*

15. Although the submitters have not experienced any explosions of alkyl azides, the substances should be treated with extreme caution.

16. The reaction was monitored by silica gel thin layer chromatography.

17. The product exhibited the following properties: R_f = 0.39 (1:4, ethyl acetate/hexanes); IR (neat): 2920, 2080, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.49 (ddd, *J* = 6.8, 9.2, 13.3 Hz, 1 H), 1.69 (ddd, *J* = 6.8, 6.8, 14.0 Hz, 1 H), 1.79–1.93 (m, 1 H), 2.46 (sextet, *J* = 6.4 Hz, 1 H), 2.85 (dd, *J* = 10.3, 15.4 Hz, 1 H), 3.11 (dd, *J* = 5.6, 15.5 Hz, 1 H), 7.15–7.23 (m, 3 H), 3.29 (dt, *J* = 1.4, 6.8 Hz, 2 H), 3.60 (d, *J* = 6.4 Hz, 2 H) 7.05–7.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5, 27.0, 34.5, 44.5, 47.0, 51.4, 126.9, 127.0, 127.9, 128.1, 133.2, 135.7, 211.0; Anal calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33; found C, 68.38; H, 6.71; N, 17.98.

18. Trifluoroacetic acid was purchased from the Aldrich Chemical Company, Inc.

19. The reaction turned purple, significant gas evolution was observed and heat was evolved during the addition of trifluoroacetic acid.

20. The product exhibited the following properties: mp 120–121 °C; R_f = 0.17 (2:3, ethyl acetate/hexanes); IR (neat): 2955, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.69–2.25 (m, 3 H), 2.18–2.31 (m, 1 H), 2.95–3.14 (m, 2 H), 3.47–3.66 (m, 3 H), 4.08–4.22 (m, 2 H), 7.02–7.22 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.0, 33.7, 39.4, 44.1, 46.7, 57.1, 127.0, 127.5, 130.3, 131.0, 132.5, 136.5, 170.0; MS (EI) *m/z* (relative intensity): 201 (M^+, 100); HRMS calcd for $C_{13}H_{15}NO$ (M^+): 201.1154, found: 201.1144. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.55; H, 7.38; N, 7.12.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although the Schmidt reaction of hydrazoic acid with ketones has been known for many years, the corresponding reaction of ketones with alkyl azides, affording *N*-substituted lactams, is of much more recent vintage.[1-4] In the 1940s, several researchers reported that the reaction of methyl azide with simple ketones using standard Schmidt reaction conditions (concentrated H_2SO_4) did not lead to any lactam products.[5,6] In the following decade, Boyer found that amides could be formed in modest yields (≤30%) when aromatic aldehydes were allowed to react with *n*-hexyl azide under H_2SO_4 promotion, but reported that these conditions failed when applied to ketones.[7] In the early 1990s, it was learned that Schmidt reactions of alkyl azides and ketones could be actuated by carrying out intramolecular reactions in δ- or ε-azido ketones.[8]

The intramolecular Schmidt reaction requires that the ketone and azide group be separated by four or five atoms (usually carbons), with the former being significantly more favorable.[8,9] Thus, Schmidt reactions of δ-azido ketones can be promoted by strong protic acids, as exemplified in the present procedure, while the homologous substrates require stronger Lewis acid promotion and are generally much more sluggish (Table 1). This is presumably because the former reactions proceed through a six-membered azidohydrin intermediate en route to products, whereas the seven-membered ring version of this intermediate is less favored (Scheme 1). In a specialized example, it was shown that advantage could be taken of the dependence of reactivity on tether length to effect a regioselective reaction in a complex example of the reaction on a diketone reactant.[10] Subsequently, it was found that the more stringent conditions used to carry out Schmidt reactions of ε-azido ketones could also be applied to intermolecular reactions of simple alkyl azides and ketones, although this reaction is of severely limited scope and frequently plagued by complicating (if sometimes interesting) side reactions.[11,12] Conversely, the intramolecular Schmidt reaction is very forgiving with respect to substitution pattern and to the nature of the reacting ketone, with successful reactions being observed to date in ketones containing from 3 to 12 members. Aldehydes also react, but can give rise to either *N*-substituted or -unsubstituted lactams depending on whether an alkyl group or a hydrogen atom migrates.

Some other features of the intramolecular Schmidt reaction are that it is highly regioselective and, where relevant, stereoselective. Thus, the product formed in a typical example of this reaction is almost always the fused lactam formed by migration of the α-carbon between the carbonyl and azide. However, a few examples of bridged adducts have been observed in specialized substrates.[10,13,14] As is common for related processes like the classical Schmidt reaction and the Baeyer–Villiger reaction, the intramolecular Schmidt reaction is stereoselective insofar as the α-carbon migrates with retention of configuration.[9] An important practical consideration, however, is that apparent loss of stereoselectivity can be observed due to the fact that the α-hydrogen is acidic and therefore this center is subject to enolization and epimerization. This is particularly problematic for sluggish substrates that require heating or extended reaction times.[15]

Scheme 1

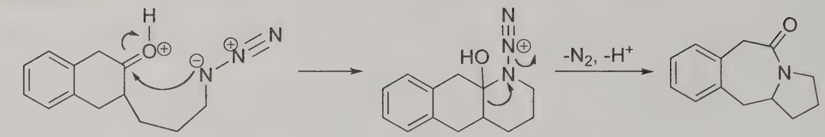
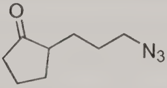
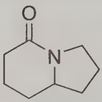
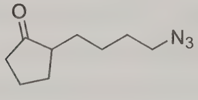
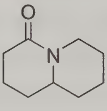
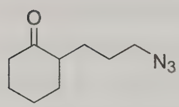
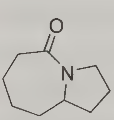
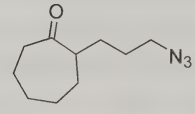
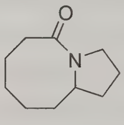
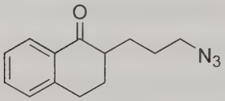
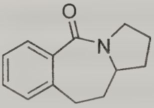
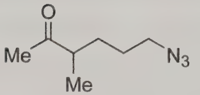
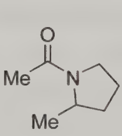
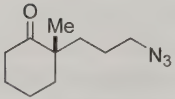
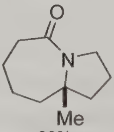
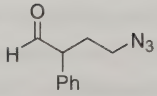
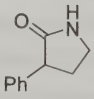


Table 1. Intramolecular Schmidt Reactions of Azido Ketones

Entry	Ketone	Product	Yield (%)
1			83
2			56
3			85
4			80
5			45
6			75
7	 91% ee	 89% ee	87
8			29

Over the same time period that saw the development of the intramolecular Schmidt reaction, a number of related processes were also reported. These included the reactions of alkyl azides with carbocations generated from alkenes[16-19] or other functional groups,[20,21] principally developed by Pearson but explored by other researchers as well. Subsequent to the discovery of the intramolecular Schmidt reaction, this laboratory has also explored the related reactions of 2- or 3-hydroxyalkyl azides with ketones, some of which can be used to effect an asymmetric nitrogen insertion reaction.[22-25] These, along with other important developments in modern alkyl azide chemistry, have been summarized in an exhaustive review article.[26]

The main utility of the present reaction is in the preparation of multicyclic nitrogen containing rings in complex alkaloid synthesis. Some targets that have been explored using this chemistry include homoerythrina alkaloids,[27] indolizidines isolated from South American frogs,[28,29] gephyrotoxin,[30] sparteine,[31] stenine,[13] and aspidospermidine.[10]

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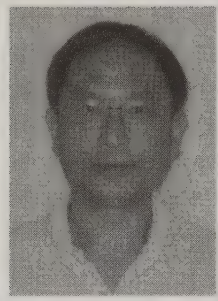
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dimethyl carbonate: Carbonic acid, dimethyl ester; (616-38-6)
Methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate: 1-Naphthalenecarboxylic acid, 1,2,3,4-tetrahydro-2-oxo-, methyl ester; (31202-23-0)
Sodium hydride; (7646-69-7)
β-Tetralone: 2(1*H*)-Naphthalenone, 3,4-dihydro-; (530-93-8)
Diisopropylamine: 2-Propanamine, *N*-(1-methylethyl)-; (108-18-9)

Butyllithium; (109-72-8)
Sodium iodide; (7681-82-5)
Sodium azide; (26628-22-8)
3-(3′-Azidopropyl)-3,4-dihydronaphthalen-2(1*H*)-one: 2(1*H*)-Naphthalenone, 3-(3-azidopropyl)-3,4-dihydro-; (137125-35-0)
Trifluoroacetic acid; (76-05-1)
2,3,11,11a-Tetrahydro-1*H*-benzo[d]pyrrolo[1,2-a]azepin-5(6*H*)-one: 5*H*-Pyrrolo[2,1-b][3]benzazepin-5-one, 1,2,3,6,11,11a-hexahydro-; (137125-37-2)

Born in the late 50s, Jeff Aubé attended the University of Miami, where he did undergraduate research with Professor Robert Gawley. He received his Ph.D. in chemistry in 1984 from Duke University, working with Professor Steven Baldwin, and was subsequently an NIH postdoctoral fellow at Yale University with Professor Samuel Danishefsky. In 1986, he moved to the University of Kansas, where he is now Professor of Medicinal Chemistry. Aubé's work involves the development of new synthetic reactions and their use in the synthesis of interesting natural products or for library generation.

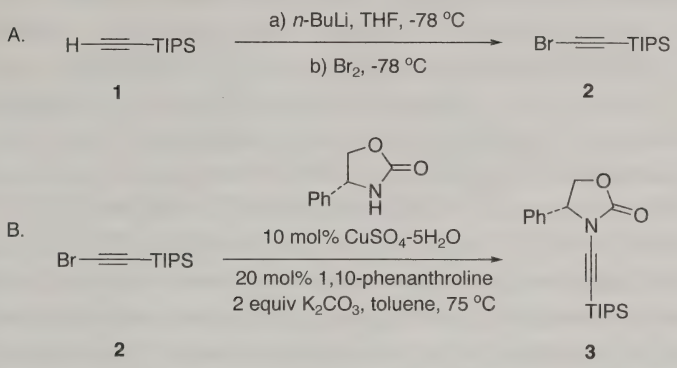
Scott Grecian was born in 1979, in Jamestown, ND. He attended Walla Walla University and received his B.S. in 2002. In the fall of 2002 he enrolled in the Department of Medicinal Chemistry at The University of Kansas and worked in the research group of Jeff Aubé, receiving his Ph.D. in 2007. His graduate research involved the investigation of double conjugate addition reactions and their application in the formal synthesis of the alkaloid natural product gelsemine.



Dalian Zhao was born in Shanghai, China and obtained his B.S. degree in Chemical Engineering from East China Institute of Chemical Engineering in 1982. He came to the United States in 1987 and earned a M.S. degree in Organic Chemistry in 1989 from the University of North Texas. He joined Merck & Co., Inc. Process Research, (Rahway, New Jersey) in 1989. He received his Ph.D. in Organic Chemistry from Rutgers University (New Brunswick) in 2000 under Professor Spenser Knapp. He is currently a Senior Research Chemist, responsible for the discovery and development of efficient and environmentally safe multistep processes, providing active pharmaceutical ingredients from gram to multi kilo scale.

PRACTICAL SYNTHESIS OF A CHIRAL YNAMIDE: (*R*)-4-PHENYL-3-(2-TRIISOPROPYLSILYL-ETHYNYL)OXAZOLIDIN-2-ONE

[2-Oxazolidinone, 4-Phenyl-3-(2-triisopropylsilyl-ethynyl)-, (4*R*)-]



Submitted by I. K. Sagamanova, K. C. M. Kurtz, and R. P. Hsung.[1]
Checked by Karen M. Marcantonio and David J. Mathre.

1. Procedures

A. 1-Bromo-2-triisopropylsilyl-ethyne (2). To a flame-dried single-necked 1-L round-bottomed flask equipped with a magnetic stir bar is added a solution of triisopropylsilylacetylene (22.0 g, 120.6 mmol) (Note 1) in anhydrous THF (500 mL) (Note 2). The solution is cooled to – 78 °C, and *n*-BuLi (50.7 mL, 126.7 mmol, 1.05 equiv) (Note 3) is added by syringe through the septum. The reaction is stirred for 30 min at – 78 °C, and Br_2 (6.80 mL, 132.7 mmol, 1.10 equiv) (Note 4) is added slowly through the septum using a syringe. The reddish brown color from Br_2 disappears as it is consumed upon addition. The solution remains reddish brown when the addition is complete. The mixture is stirred for 15 min at –78 °C and then quenched by addition of saturated aqueous $Na_2S_2O_3$ (150 mL) after removal of the septum. The reaction mixture is transferred to a separatory funnel and the layers separated. The aqueous layer is further extracted with methyl *tert*-butyl ether (MTBE) (3 × 50 mL), and the combined organic extracts are washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered and concentrated on a rotary evaporator (20 – 30 mmHg, 50 °C) to yield the

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crude alkynyl bromide **2** (30.22–30.24 g, 96%) as a pale yellow oil (Note 5). Alkynyl bromide **2** is used without further purification (Note 6).

B. (R)-4-Phenyl-3-(2-triisopropylsilyl-ethynyl)oxazolidin-2-one (3). To a solution of 1-bromo-2-triisopropylsilylacetylene (**2**) (28.19 g, 107.9 mmol) (Note 7) in freshly distilled anhydrous toluene (100 mL) (Note 2) in a 250-mL, single-necked, round-bottomed flask fitted with a magnet stir bar are added *R*-phenyloxazolidinone (17.60 g, 107.9 mmol, 1.00 equiv) (Note 8), K_2CO_3 (29.81 g, 215.7 mmol, 2.00 equiv) (Note 9), $CuSO_4 \cdot 5H_2O$ (2.69 g, 10.8 mmol, 0.10 equiv) (Note 10), and 1,10-phenanthroline (3.89 g, 21.6 mmol, 0.20 equiv) (Note 11). The flask is fitted with a reflux condenser topped with a septum and N_2 inlet, and heated in an oil bath at 75 °C (bath temperature) for 48 h. The reaction is monitored using TLC analysis (Note 12). Upon completion, the reaction mixture is cooled to room temperature and filtered through a 200-mL coarse-fritted vacuum filtration funnel containing a 5-cm layer of silica gel covered with a 1-cm layer of Celite. The mixture is washed through with 50% EtOAc/hexanes (400 mL), and the filtrate is concentrated on a rotary evaporator (20 – 30 mmHg, 70 °C). The crude residue is purified using silica gel column flash chromatography (Note 13) to give ynamide **3** (29.5–32.7 g, 81–88%) (Notes 14 and 15) as a yellow oil.

2. Notes

1. Triisopropylacetylene (97%) was purchased from GFS Chemicals.

2. Anhydrous solvents were obtained from an MBraun solvent purification system. Unstabilized THF was purchased from JT Baker, and toluene was purchased from Aldrich.

3. *N*-Butyllithium (2.5 *M* solution in hexanes) was purchased from Aldrich Chemical Co.

4. Bromine (99+%) was purchased from Fisher Scientific.

5. Characterization of **2**: R_f = 0.72 [25% EtOAc in hexanes]; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06–1.10 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 18.4, 61.6, 83.4.

6. This purification step was not necessary~~,~~ because, in most cases, high purity was obtained judging from ^{1}H NMR. However, product **2** was stable to silica gel column flash chromatography and could be eluted with hexanes. Other alkynyl bromides may require silica gel column flash chromatography for purification.

7. The amidation reaction was performed successfully on a variety of scales [see Discussion section].

8. *R*-Phenyloxazolidinone (98%) was purchased from Aldrich and used as received.

9. Potassium carbonate (98%; ~ 325 mesh powder) was purchased from Aldrich.

10. $CuSO_4 \cdot 5H_2O$ (99.3%) was purchased from J. T. Baker. The solid was ground into a powder with a mortar and pestle before use.

11. 1,10-Phenanthroline (99+%) was purchased from Aldrich. The solid was ground into a powder with a mortar and pestle before use.

12. TLC analysis (25% EtOAc/hexanes): R_f(oxazolidinone) = 0.03, R_f(**2**) = 0.72, R_f(**3**) = 0.39.

13. The crude product was dissolved in 200 mL of CH_2Cl_2 in a round-bottomed-flask, and 75 g silica gel was added to the flask. The CH_2Cl_2 was removed on a rotary evaporator (20–30 mmHg, 35 °C) equipped with a bump trap. The dried contents of the flask were loaded onto the column (size $l \times d$ = 30 cm × 5 cm) containing a slurry of silica gel and hexanes layered with sand. Gradient elution [EtOAc in hexanes]: 800 mL 0%, 800 mL 2%, 1000 mL 5%, 1500 mL 7%, 2000 mL 10%.

14. GC analysis of ynamide **3** shows its purity to be ≥98.0%.

15. Characterization of **3**: R_f = 0.39 [25% EtOAc in hexanes]; clear oil; $[\alpha]_D^{23}$ – 133.7 (c 1.21, CH_2Cl_2); Chiralcel OD-H (250 x 4.6 mm), 5% IPA/heptane, 1.0 mL/min, 215 nm, t_R (*R*) 10.77 min, t_R (*S*) 13.66 min: >99.5 % ee R. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90–0.93 (m, 21 H), 4.28 (dd, 1 H, *J* = 7.6, 8.8 Hz), 4.73 (t, 1 H, *J* = 8.8 Hz), 5.06 (dd, 1 H, *J* = 7.6, 8.8 Hz), 7.34–7.45 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.0, 18.3, 62.2, 70.4, 71.9, 91.8, 127.1, 129.1, 129.4, 135.7, 155.2; IR (thin film) cm^{-1} 2943 (m), 2185 (w), 1782 (s), 1394 (m), 883 (m); mass spectrum (APCI): *m/z* (% relative intensity) 344 (13) $(M + H)^+$, 334 (33), 318 (100); *m/z* calcd for $C_{20}H_{29}NO_2Si$ 344.2040, found 344.2047

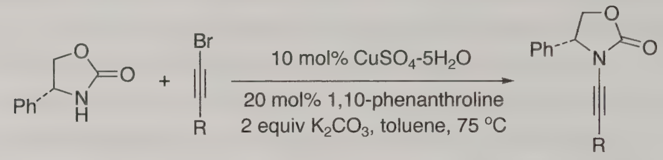
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

It is note worthy that this cooper-catalyzed amidation of alkynyl bromide can be carried out with scales ranging from 48 to 107 mmol. The respective ynamide products were isolated with yields ranging from 86–89 %.

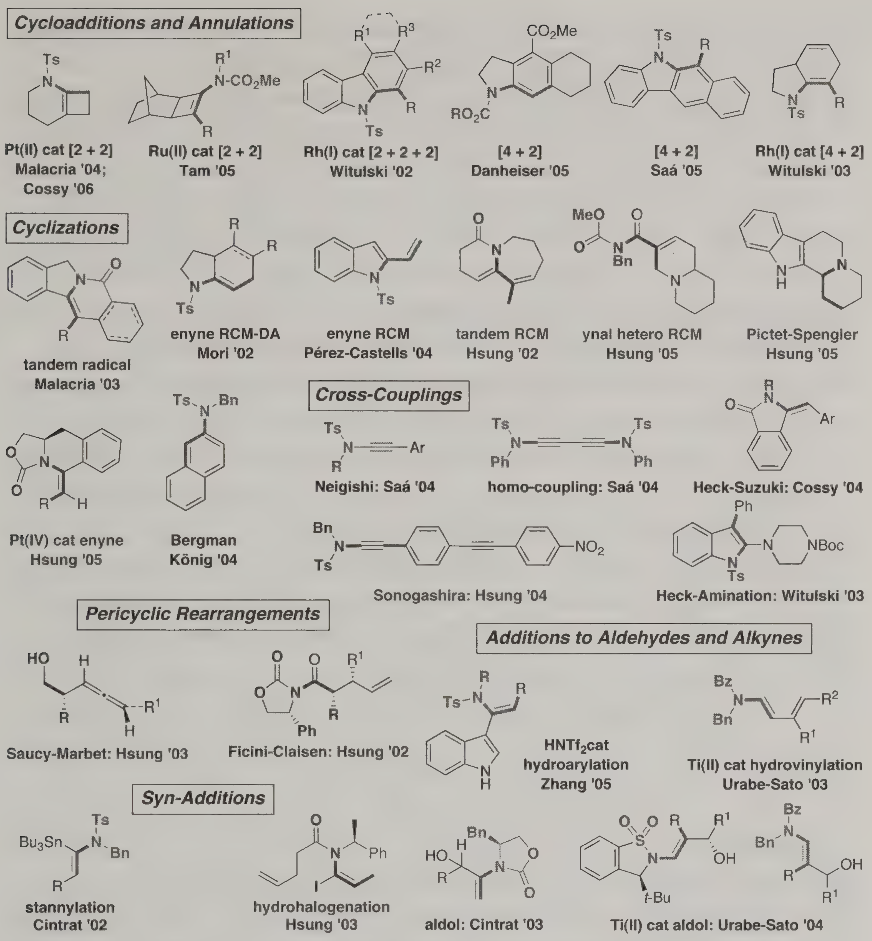
Table 1


Ph
N
H
O
O
+
Br
R
10 mol% $CuSO_4$-$5H_2O$
20 mol% 1,10-phenanthroline
2 equiv K_2CO_3, toluene, 75 °C
Ph
O
N
O
R

halide	R =	scale [mmols]	product	isolated yield [%, g]
2a	TIPS	48	**3a**	89 [14.63 g]
	TIPS	107		86 [32.07 g]
2b	Ph	18	**3b**	60 [4.66 g]
	Ph	35		71 [6.72 g]

The level of purity of the ynamides prepared using this procedure can be unambiguously established using GC/HPLC analysis for ynamide **3**. The level of optical purity of the product is dependent upon the optical purity of the chiral auxiliaries acquired from commercial sources. The $[\alpha]_D^{20}$ value for the commercial (*R*)-2-phenyloxazolidinone used in this preparation was –52.3 [c 2.0, $CHCl_3$]. The $[\alpha]_D^{20}$ values reported by Aldrich for (*R*)-2-phenyloxazolidinone and (*S*)-2-phenyloxazolidinone are –48.0 [c 2.0, $CHCl_3$], which indicates that the *ee* or optical integrity of the Evans' auxiliary used for this work was very high. Severe erosion of the auxiliary's *ee* is unlikely under the amidation conditions described herein. The anticipated high *ee* of chiral ynamide (*R*)-**3** was confirmed by chiral HPLC.

Ynamides[2-9] have become a highly attractive building block for developing synthetic methodologies.[10-11] As illustrated in Figure 1, there have been at least 30 reports in the last few years describing dozens of different strategies employing ynamides. Particularly attractive are those in which the nitrogen atom of ynamides becomes an integral part of various products that possess potential in alkaloid synthesis. These efforts demonstrate that there can be a distinct advantage in utilizing ynamides over simple alkynes. Therefore, the key issue, in part being addressed in this *Organic Syntheses* procedure, is their preparation. We, as well as others, have exerted much effort toward this goal.[3-9]


Cycloadditions and Annulations
Pt(II) cat [2 + 2] Malacria '04; Cossy '06
Ru(II) cat [2 + 2] Tam '05
Rh(I) cat [2 + 2 + 2] Witulski '02
[4 + 2] Danheiser '05
[4 + 2] Saá '05
Rh(I) cat [4 + 2] Witulski '03
Cyclizations
tandem radical Malacria '03
enyne RCM-DA Mori '02
enyne RCM Pérez-Castells '04
tandem RCM Hsung '02
ynal hetero RCM Hsung '05
Pictet-Spengler Hsung '05
Pt(IV) cat enyne Hsung '05
Bergman König '04
Cross-Couplings
Neigishi: Saá '04
homo-coupling: Saá '04
Heck-Suzuki: Cossy '04
Sonogashira: Hsung '04
Heck-Amination: Witulski '03
Pericyclic Rearrangements
Saucy-Marbet: Hsung '03
Ficini-Claisen: Hsung '02
Additions to Aldehydes and Alkynes
HNTf2cat hydroarylation Zhang '05
Ti(II) cat hydrovinylation Urabe-Sato '03
Syn-Additions
stannylation Cintrat '02
hydrohalogenation Hsung '03
aldol: Cintrat '03
Ti(II) cat aldol: Urabe-Sato '04

1. School of Pharmacy, University of Wisconsin, 777 Highland Ave., Madison, Wisconsin 53705-2222 USA.
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9. Also see: Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 906.
10. For an impressive array of reports on the chemistry of ynamides just in the last three years, see: (a) For a special issue dedicated to the chemistry of ynamides, see: *Tetrahedron-Symposium-In-Print:* "Chemistry of Electron-Deficient Ynamines and Ynamides." *Tetrahedron* **2006**, *62*, Issue No.16. (b) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586. (c) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726. (d) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (e) Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 6483. (f) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (g) Martinez-Esperon, M. F.; Rodriguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213. (h) Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, *7*, 783. (i) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (j) Rosillo, M.; Domínguez, G.; Casarrubios,L.; Amador, U.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*,

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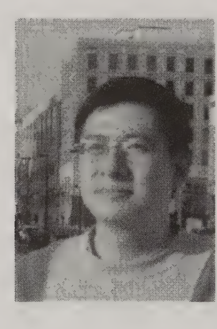
11. For our own recent applications of ynamides, see: (a) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Chem. Commun.* **2007**, *ASAP*. (b) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, *ASAP*. (c) You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, *in press*. (d) Tracey, M. R.; Oppenheimer, J.; Hsung, R. P. *J. Org. Chem.* **2006**, *71*, 8629. (e) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Syn. Cat.* **2006**, *348*, 2437. (f) Zhang, X.; Hsung, R. P.; You, L. *Organic Biomol. Chem.* **2006**, *6*, 2679. (g) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (h) Kurtz, K. C. M.; Frederick, M. O.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 3928. (i) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Organic Lett.* **2006**, *8*, 231. (j) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A.; *Org. Lett.* **2005**, *7*, 1047. (k) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209. (l) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353. (m) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663. (n) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H. A.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547. (o) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar. C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (p) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383.

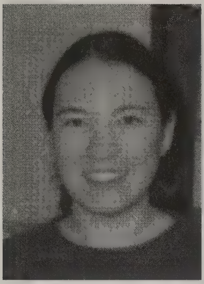
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

n-Butyllithium: Butyllithium; (109-72-8)
Triisopropylsilylacetylene: Silane, ethynyltris(1-methylethyl)-; (89343-06-6)
Copper sulfate pentahydrate; (7758-99-8)
1-Bromo-2-triisopropylsilyl-ethyne: Silane, (bromoethynyl)tris(1-methylethyl)-; (111409-79-1)
R-Phenyloxazolidinone: (4*R*)-4-Phenyl-2-Oxazolidinone; (90319-52-1)
1,10-Phenanthroline; (66-71-7)



Richard P. Hsung was born in China in 1966. After growing up in New York City and Boston, he obtained his B.S. in Chemistry and Mathematics in 1988 from Calvin College. He attended The University of Chicago and received his Ph.D. degree in Organic Chemistry in 1994, under the supervision of Professors Jeff Winkler and Bill Wulff. He completed his training as an NIH post-doctoral fellow in Professor Gilbert Stork's laboratory at Columbia University. In 1997, he began his academic career at the University of Minnesota, moving to University of Wisconsin at Madison in 2006. He is a recipient of numerous awards including the Camille Dreyfus Teacher-Scholar Award and National Science Foundation Career Award. His current research focuses on the development of cycloaddition and annulation strategies to natural product syntheses.

Irina K. Sagamanova was born in Noyabrsk, Russia, in 1985, and received a B.S. in Chemistry from The Higher Chemical College Russia Academy of Science in Moscow in 2006. She went to University of Minnesota and worked in Professor Richard P. Hsung's research group during the summer of 2005. Her research involves improving synthesis of chiral ynamides and exploring their reactivities.



Kimberly C. M. Kurtz was born in Findlay, OH, in 1979, and received a B.S. in Chemistry from Ohio Northern University, Ada, OH in 2001. Her father, David Kurtz, was a long time Organic Chemistry faculty at ONU. She enrolled at University of Minnesota-Twin Cities and worked in Professor Richard P. Hsung's laboratory. Her research involved improving synthesis of chiral ynamides and exploring their reactivity in various pericyclic and ring-closing reactions. In 2006, she obtained her Ph.D. in Organic Chemistry, and is currently a senior scientist in the Corporate Research Laboratory at 3M in Saint Paul, MN.

Karen Marcantonio was born and raised in Cranston, RI. She earned her BS in chemistry in 1997 at Connecticut College, doing research under Dr. Timo Ovaska and Dr. Bruce Branchini. After a summer internship at Pfizer, she began graduate school at UPenn, earning her masters from Marisa Kozlowski in 1999. She has been working in Merck Process Research since November 1999.

ERRATA

FACILE SYNTHESES OF AMINOCYCLOPROPANES: *N,N*-DIBENZYL-*N*-(2-ETHENYLCYCLOPROPYL)AMINE

A. de Meijere, H. Winsel, and B. Stecker

The amount of titanium tetrachloride and the concentration of methylithium solution were incorrectly recorded in the original published version of this *Organic Syntheses* procedure (*Org. Synth.* **2004**, *81*, 14) due to typographical errors. The correct amount of titanium tetrachloride is 5.48 mL and the correct concentration of methyl lithium in ether is 1.6 M. A corrected version of this procedure is available on the *Organic Syntheses* website (orgsyn.org).

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CUMULATIVE SUBJECT INDEX FOR VOLUMES 80-84

This index comprises subject matter for Volumes **80**, **81**, **82, 83** and **84.** For subjects in previous volumes, see either the indices in Collective Volumes I through X or the single volume entitled *Organic Syntheses, Collective Volumes I-VIII, Cumulative Indices,* edited by J. P. Freeman.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to Chemical Abstracts nomenclature, accompanied by its registry number in parentheses. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

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5-Bromo-*m*-xylene: Benzene, 1-bromo-3,5-dimethyl-; (556-96-7) **84**, 163
(*R*)-BUTAN-2-ONE, 1-CYCLOHEXYL, 1-HYDROXY-; (512785-95-4) **84**, 111
3-Butenylmagnesium bromide: Magnesium, bromo-3-butenyl-(8,9); (7013-09-5), **81**, 17
(2S-*trans*)-2-*tert*-Butoxycarbonylacetyl-4-hydroxypyrrolidine-1-carboxylic acid, *tert*-butyl ester: 2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-4-hydroxy-β-oxo-,1,1-dimethylethyl ester, [2*S*-*trans*]- (9); (167963-29-3), **81**, 178
(*R*)-(*N*-*tert*-BUTOXYCARBONYL)ALLYLGLYCINE: 4-Pentenoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-, (2*R*)-; (170899-08-8), **80**, 31
(3*R*,5*R*,6*S*)-4-*tert*-Butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'-enyl)morpholin-2-one: 4-Morpholinecarboxylic acid, 2-oxo-5,6-diphenyl-3-(2-propenyl)-, 1,1-dimethylethyl ester, [3*R*-(3*a*,5*b*,6*b*)]-; (143140-32-3), **80**, 31
2(*S*)-(β-*tert*-BUTOXYCARBONYL-α-(*R*)-HYDROXY)ETHYL-4(*R*)-HYDROXYPYRROLIDINE-1-CARBOXYLIC ACID, *tert*-BUTYL ESTER: (2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-β,4-dihydroxy-, 1,1-dimethylethyl ester, [2*S*-[2α(S*),4*b*]]-; (167963-30-6), **81**, 178

2(*S*)-(β-*tert*-BUTOXYCARBONYL-α-(*S*)-HYDROXY)ETHYL-4(*R*)-HYDROXYPYRROLIDINE-1-CARBOXYLIC ACID, *tert*-BUTYL ESTER, **81**, 178

N-(*tert*-BUTOXYCARBONYL)- L-IODOALANINE METHYL ESTER: L-Alanine, *N*-[(1,1-dimethylethoxy)carbonyl]-3-iodo-, methyl ester; (93267-04-0), **81**, 77

N-(*tert*-BUTOXYCARBONYL)- L-4-(METHOXYCARBONYL)PHENYL]ALANINE METHYL ESTER: L-Phenylalanine,*N*-[(1,1-dimethylethoxy)carbonyl]-4-(methoxycarbonyl)-, methyl ester (9); (160168-19-4), **81**, 77

tert-Butoxycarbonyl- L-proline: 1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester, (*S*)-*tert*-Butoxycarbonyl- L-proline (15761-39-4) **83**, 70

(*S*)-*N*-(*N*-*tert*-Butoxycarbonylprolyl)dihydroisoindole (188122-39-6) **83**, 70

N-(*tert*-Butoxycarbonyl)- L-serine methyl ester: L-Serine, *N*-[(1,1-dimethylethoxy)carbonyl]-, methyl ester (9); (2766-43-0), **81**, 77

(*S*)-*N*-(*tert*-Butoxycarbonyl)valine methyl ester: Valine, *N*-[(1,1-dimethylethoxy)carbonyl]-, methyl ester, (*S*)-; (58561-04-9), **80**, 57

(*S*)-*N*-(*tert*-Butoxycarbonyl)valine: Valine, *N*-[(1,1-dimethylethoxy)carbonyl]-; (13734-41-3), **80**, 57

tert-Butyl acetate: Acetic acid, 1,1-dimethylethyl ester; (540-88-5), **81**, 179

n-Butyl acrylate: 2-Propenoic acid, butyl ester; (141-32-2), **80**, 172

n-Butylamine: 1-Butanamine; (109-73-9) **84**, 77

tert-Butylamine: 2-Propanamine, 2-methyl-; (75-64-9) **84**, 163

(R_S)-(+)-*tert*-Butyl *tert*-butanethiosulfinate: 2-Propanesulfinothioic acid, 2-methyl-, *S*-(1,1-dimethylethyl) ester, [*S*(*R*)]-; (67734-35-4) **82**, 157

tert-Butyldichlorophosphine: Phosphonous dichloride, (1,1-dimethylethyl)-; (25979-07-1) **82**, 22

n-BUTYL 2,2-DIFLUOROCYCLOPROPANECARBOXYLATE: Cyclopropanecarboxylic acid, 2,2-difluoro-, butyl ester; (260352-79-2), **80**, 172

tert-Butyldimethylphosphine)trihydroboron: Boron, [(1,1-dimethylethyl)dimethylphosphine]-trihydro-; (203000-43-5) **82**, 22

tert-Butyldimethylsilyl chloride; Silane, chloro(1,1-dimethylethyl)dimethyl- (9); (18162-48-6), **81**, 157; **83**, 155

(*tert*-Butyldimethylsilyloxy)acetaldehyde: Acetaldehyde, [[(1,1-dimethylethyldimethylsilyl]oxy]-; (102191-92-4) **82**, 34

1-(*tert*-BUTYLDIMETHYLSILYLOXY)-8-(METHOXYCARBONYL)-6-METHYLBICYCLO [4.2.0]OCTANE: Bicyclo[4.2.0]octane-7-carboxylic acid, 6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methyl-, methyl ester, (1*R*,6*R*,7*S*)-rel-: (657428-75-6) **83**, 193

1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene: Silane, (1,1-dimethylethyl)[(1-methoxyethenyl)oxy]dimethyl- (9); (77086-38-5) **84**, 272

1-*tert*-Butyldimethylsilyloxy-2-methyl-1-cyclohexene: Silane, (1,1-dimethylethyl)dimethyl[(2-methyl-1-cyclohexen-1-yl)oxy]-; (20152-33-4) **83**, 193

(*S*)-4-(*tert*-BUTYLDIMETHYLSILYLOXY)-2-PENTYN-1-OL, **81**, 157
  ee determination, **81**, 164

(*S*)-2-(*tert*-Butyldimethylsilyloxy)propanal: Propanal, 2-[[(1,1-dimethylethyl)dimethyl silyl]oxy]-, (2*S*)-; (87727-28-4), **81**, 159

3-BUTYL-2-FLUORO-1-TOSYLINDOLE: 1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-; (195734-36-2) **83**, 111

1-(*TERT*-BUTYLIMINO-METHYL)-1,3-DIMETHYL-UREA HYDROCHLORIDE **82**, 59

tert-Butyl isocyanide: Propane, 2-isocyano-2-methyl-; (7188-38-7) **82**, 59

n-Butyllithium: Lithium, butyl-; (109-72-8) **80**, 160; **81**, 2, 43, 44, 89, 112, 134, 159; **82**, 43, 147; **84**, 163, 272, 306, 347, 359
sec-Butyllithium: Lithium, (1-methylpropyl)-; (598-30-1), **80**, 46; **82**, 22
tert-Butyllithium; Lithium, (1,1-dimethylethyl)-; (594-19-4), **81**, 122; **84**, 120
n-Butylmagnesium chloride: Magnesium, butylchloro-; (693-04-9), **80**, 111
Butyl methacrylate: 1-Propenoic acid, 2-methyl-, butyl ester; (97-88-1), **81**, 63
1-Butyl-3-methylimidazolium chloride: *1H*-Imidazolium, 1-butyl-3-methyl-, chloride; (79917-90-1) **82**, 166
1-Butyl-3-methylimidazolium tetrafluoroborate: *1H*-Imidazolium, 1-butyl-3-methyl, tetrafluoroborate (1–); (174501-65-6) **82**, 166
(5*S*,6*R*)-4-*tert*-BUTYLOXYCARBONYL-5,6-DIPHENYLMORPHOLIN-2-ONE: 4-Morpholinecarboxylic acid, 6-oxo-2,3-diphenyl-, 1,1-dimethylethyl ester, (2*R*-*cis*)-;(173397-90-5), **80**, 18, 31
(5*R*,6*S*)-4-*tert*-BUTYLOXYCARBONYL-5,6-DIPHENYLMORPHOLIN-2-ONE: 4-Morpholinecarboxylic acid, 6-oxo-2,3-diphenyl-, 1,1-dimethylethyl ester, (2*S*-*cis*)-;(112741-50-1), **80**, 18
1-*tert*-BUTYLOXYCARBONYL-4-(9-FLUORENYLMETHYLOXYCARBONYLAMINO)PIPERIDINE-4-CARBOXYLIC ACID: 1,4,Piperidinedicarboxylic acid, 4-[[(*9H*-fluoren-9-ylmethyloxy)-carbonyl]amino]-, 1-(1,1-dimethylethyl)ester; (183673-66-7), **81**, 213
1-*tert*-Butyloxycarbonylpiperidine-4-spiro-5'-(1',3'-bis(*tert*-butyloxycarbonyl) hydantoin: 1,3,8-Triazaspiro[4.5]decane-1,3,8-tricarboxylic acid, 2,4-diiso-, tris(1-dimethylethyl)ester; (183673-68-9), **81**, 214
tert-Butyl phenyl carbonate: Carbonic acid, 1,1-dimethylethyl phenyl ester; (6627-89-0) **84**, 209
(*R*)-3-Butyn-2-yl mesylate: 3-Butyn-2-ol, methanesulfonate, (2*R*)-; (121882-95-4) **82**, 43

anti-(1*R*)-(1)-Camphorquinone 3-oxime: 1,7,7-Trimethyl-bicyclo[2.2.1]heptane-2,3-dione 3-oxime; (31571-14-9) **82**, 87
(±)-10-Camphorsulfonic acid; (5872-08-2) **84**, 32
D-(+)-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1*S*,4*R*)-; (3144-16-9), **80**, 66
(1*R*)-(+)-Camphor: 1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one; (464-49-3) **82**, 87
Carbazole: 9H-Carbazole; (86-74-8) **84**, 177
CARBAZOLE-BASED TETRAKISMACROCYCLE; (245648-36-6) **84**, 177
(η^5-Carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt; (182627-81-2) **84**, 139
(2-Carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide: Phosphonium, [[2-(methoxycarbonyl)-6-nitrophenyl]methyl]triphenyl-, bromide; (195992-09-7), **80**, 75
Carbon dioxide; (124-38-9), **80**, 46
Carbon monoxide; (630-08-0), **80**, 75, 93
Carbon tetrabromide: Methane, tetrabromo-; (558-13-4), **81**, 1
Carbon tetrachloride: Tetrachloromethane; (56-23-5) **82**, 93
Carbonyldihydridotris(triphenylphosphine)ruthenium(II): Ruthenium, carbonyldihydridotris(triphenylphosphine); (25360-32-1), **80**, 104
Carbonyldiimidazole: 1*H*-Imidazole, 1,1'-carbonylbis-; (530-62-1) **84**, 233
2-Carboxyethyltriphenylphosphonium chloride; (36626-29-6) **84**, 334

Catalytic reduction **82**, 1
Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7) **83**, 24
Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8) **82**, 69; **84**, 215, 272
Cesium hydroxide: Cesium hydroxide (CsOH); (21351-79-1), **80**, 38
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Chloroacetyl chloride: Acetyl chloride, chloro-; (79-04-9), **80**, 200
2-CHLOROACROLEIN DIETHYL ACETAL: 1-Propene, 2-chloro-3,3-diethoxy-; (7575-33-9)
Chlorobenzene: Benzene, chloro-(8,9); (108-90-7), **81**, 64
4-Chlorobenzoic acid methyl ester: Benzoic acid, 4-chloro-, methyl ester; (1126-46-1), **81**, 34
4-Chlorobenzonitrile: Benzonitrile, 4-chloro- (9); (623-03-0), **81**, 64
2-CHLORO-1,3-BIS(DIMETHYLAMINO)TRIMETHINIUM HEXAFLUOROPHOSPHATE: Methanaminium, *N*-[2-chloro-3-(dimethylamino)- 2-propenylidene]-*N*-methyl-, hexafluorophosphate(1-); (249561-98-6), **80**, 207
(*S*)-1-Chloro-3-(Boc-amino)-4-phenyl-2-butanone: Carbamic acid, [(*1S*)-3-chloro-2-oxo-1-(phenylmethyl)propyl]-, 1,1-dimethylethyl ester; (102123-74-0) **84**, 58
2-Chloro-1-decen-3-yne; (534600-74-3) **84**, 77
1-CHLORO-4-(2,2-DICHLORO-1-METHYLVINYL)BENZENE: Benzene, 1-chloro-4-(2,2-dichloro-1-methylethenyl)-; (73644-88-9) **82**, 93
Chlorodimethylsilane; (1066-35-9) **83**, 38
Chlorodimethylphenylsilane; (768-33-2) **84**, 22
1-Chloro-3-iodobenzene; (625-99-0) **82**, 126
2-Chloro-5-iodopyridine; (69045-79-0) **84**, 215
1-CHLORO-3-IODO-5-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)BENZENE: (2-(3-Chloro-5-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; (479411-94-4) **82**, 126
m-Chloroperbenzoic acid; Benzenecarboperoxoic acid, 3-chloro-; (937-14-4), **80**, 207
2-Chloropyridine; (109-09-1) **84**, 295
2-Chloro-3-pyridinecarboxaldehyde; (36404-88-3) **84**, 262
9-Chloromethylanthracene: Anthracene, 9-(chloromethyl)-; (24463-19-2), **80**, 38
CHLOROMETHYL METHYL ETHER: Methane, chloromethoxy-; (107-30-2) **84**, 102
1-(4-Chlorophenyl)ethanone; (99-91-2) **82**, 93
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3-Chloropropionic acid: Propanoic acid, 3-chloro-; (107-94-8) **84**, 334
N-Chlorosuccinimide: 2,5-Pyrrolidinedione, 1-chloro-; (128-09-6), **80**, 133
Chlorotitanium triisopropoxide: Titanium, chlorotris(2-propanolato)-, (T-4)-; (20717-86-6), **80**, 111
Chlorotriethylsilane: Silane, chlorotriethyl-; (994-30-9) **83**, 61
N-1-(Chloro-2,2,2-trifluoroethyl)acetamide; (6776-46-1) **84**, 32
Chlorotrimethylsilane: Silane, chlorotrimethyl- (9); (75-77-4) **80**, 172; **81**, 26, 216; **83**, 61; **84**, 285
Chlorotris(triphenylphosphine)cobalt(I); (26305-75-9) **84**, 139
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Chromium trioxide; (1333-82-0) **84**, 199

Cinchonidine: Cinchonan-9-ol, (8a, 9*R*)-; (485-71-2), **80**, 38
R-(+)-Citronellal: 6-Octenal, 3,7-dimethyl-, (3*R*)-; (2385-77-5), **80**, 195
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2,4,6-Collidine: Pyridine, 2,4,6-trimethyl-; (108-75-8) **84**, 139
(*S*)-COP-Cl: COBALT, BIS[1,1',1",1'"-(**η**4-1,3-CYCLOBUTADIENE-1,2,3,4-TETRAYL)TETRAKIS[BENZENE]](di-**μ**-CHLORODIPALLADIUM)BIS[**μ**-[(1-**η**:1,2,3,4,5-**η**)-2-[(4*S*)-4,5-DIHYDRO-4-(1-METHYLETHYL)-2-OXAZOLYL-**κ***N*3]-2,4-CYCLOPENTADIEN-1-YL]]DI-; (581093-92-7) **82**, 134; **84**, 148
(*S*)-COP-hfacac: HEXAFLUOROACETYLACETONATE[(η^5-(*S*)-(*pR*)-2-(2'-(4'-METHYLETHYL)OXAZOLINYL)CYCLOPENTADIENYL, 1-*C*, 3'-*N*)(η^4-TETRAPHENYLCYCLOBUTADIENE)COBALT] PALLADIUM; (805315-08-6) **84**, 148
(*S*)-COP-OAc: Di-*μ*-ACETATOBIS[(η^5-(*S*)-(*pR*)-2-(2'-(4'-METHYLETHYL)OXAZOLINYL)CYCLOPENTADIENYL, 1-*C*, 3'-N)(η^4-TETRAPHENYLCYCLOBUTADIENE)COBALT] DIPALLADIUM; (849592-74-1) **84**, 148
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Copper(II) acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate; (6046-93-1) **82**, 108
Copper(I) bromide; (7787-70-4) **84**, 1
Copper (I) chloride: Copper chloride: (7758-89-6) **82**, 69, 93
Copper (II) chloride: Copper chloride; (7447-39-4) **82**, 22
Copper(I) Iodide: Copper iodide (CuI); (7681-65-4), **80**, 129; **84**, 77, 88, 177, 192
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1,4-Cyclohexanedione mono-ethylene ketal: 1,4-Dioxaspiro[4.5]decan-8-one; (4746-97-8) **84**, 233
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Cyclohexylamine: Cyclohexanamine; (108-91-8), **80**, 93
2-(Dicyclohexylphosphino)biphenyl: Phosphine, [1,1'-biphenyl]-2-yldicyclohexyl-; (247940-06-3) **84**, 163
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2-Cyclopenten-1-one; (930-30-3), **80**, 144
2-CYCLOPENTYLACETOPHENONE: Ethanone, 2-cyclopentyl-1-phenyl-; (23033-65-0), **81**, 121
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1,3-DECADIYNE; (55682-66-1) **84**, 77, 88
1-Decanol: 1-Decanol (9); (112-30-1) **82**, 80
Decanal: Decanal (8,9); (112-31-2) **82**, 80
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3,6-DIACETYL-9,10-DIMETHOXYPHENANTHRENE: Ethanone, 1,1'-(9,10-dimethoxy-3,6-phenanthrenediyl)bis-; (310899-08-2), **80**, 227, 233
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(*R,R*)-Dibenzofuran-4,6-dicarboxylic acid bis(2-hydroxy-1-phenylethyl)amide: 4,6-Dibenzofurandicarboxamide, *N,N'*-bis[(1*R*)-2-hydroxy-1-phenylethyl]-; (247097-79-6), **80**, 46
(*R,R*)-4,6-DIBENZOFURANDIYL-2,2'-BIS(4-PHENYLOXAZOLINE) (DBFOX/PH): Oxazole, 2,2'-(4,6-dibenzofurandiyl)bis(4,5-dihydro-4-phenyl-, (4*R*,4'*R*)-; (195433-00-2), **80**, 46
Dibenzoylmethane: 1,3-Propanedione, 1,3-diphenyl-: (120-46-7) **84**, 222
Dibenzoyl peroxide: Peroxide, dibenzoyl; (94-36-0), **80**, 75
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(*R*)-(+)-*N,N*-Dibenzyl-*N*-[1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-amine: Benzenemethanamine, *N*-[(1*R*)-1-cyclohexyl-3-(trimethylsilyl)-2-propynyl]-*N*-(phenylmethyl)-; (872357-80-7) **84**, 1

N,N-DIBENZYL-*N*-(2-ETHENYLCYCLOPROPYL)AMINE: BENZENEMETHANAMINE, N-(2-ETHENYLCYCLOPROPYL)-*N*-(PHENYLMETHYL)-; (220247-75-5), **81**, 14
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(4,4-Dibromobut-3-enyl)benene: Benzene, (4,4-dibromo-3-butenyl)-; (119405-97-9), **81**, 1
3,4-Dibromo-2,5-diformylthiophene: 2,5-Thiophenedicarboxaldehyde, 3,4-dibromo-; (25373-20-0) **83**, 209
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2-Mesitylmagnesium bromide: Magnesium, bromo(2,4,6-trimethylphenyl)-; (2633-66-1) **83**, 131

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1-Methoxy-1,3-butadiene: 1,3-Butadiene, 1-methoxy-; (3036-66-6) **82**, 34

(Methoxycarbonylmethylene)triphenylphosphorane: Phosphonium, triphenyl-, 2-methoxy-2-oxoethylide; (21204-67-1) **82**, 140

N-(Methoxycarbonyl)-2-propenylamine: Carbamic acid, 2-propenyl-, methyl ester; (19364-21-7) **84**, 88

1-METHOXY-2-(4-METHOXYPHENOXY)BENZENE **82**, 69

1-METHOXYMETHOXY-1-PHENYLETHANE: Benzene, [1-(methoxymethoxy)ethyl]-; (94073-86-6) **84**, 102

N-Methoxy-*N*-methylcarbamoyl chloride: Carbamic chloride, methoxymethyl-; (30289-28-2) **82**, 147

[1-(METHOXYMETHYLCARBAMOYL)ETHYL]PHOSPHONIC ACID BIS-(2,2,2-TRIFLUOROETHYL) ESTER: Phosphonic acid, [2-(methoxymethylamino)-1-methyl-2-oxoethyl]-, bis(2,2,2-trifluoroethyl) ester; (448219-33-8) **82**, 147

4-Methoxyphenacyl bromide; Ethanone, 2-bromo-1-(4-methoxyphenyl)-; (2632-13-5), **81**, 105

4-Methoxyphenethyl alcohol: Benzeneethanol, 4-methoxy-; (702-23-8), **81**, 195

4-Methoxyphenol: Phenol, 4-methoxy-; (150-76-5) **82**, 55, 69

4-METHOXYPHENYLACETIC ACID: BENZENEACETIC ACID, 4-METHOXY-; (104-01-8) **81**, 195

4-(4-METHOXYPHENYL)-2-PHENYL-1H-IMIDAZOLE: *1H*-IMIDAZOLE, 4-(METHOXYPHENYL)- 2-PHENYL-; (53458-08-5), **81**, 105

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1-Methoxy-4-vinyloxybenzene **82**, 55

Methyl acrylate: 2-Propenoic acid, methyl ester; (96-33-3), **80**, 38; **83**, 162, 193

Methyl azidoacetate: Acetic acid, azido-, methyl ester; (1816-92-8) **84**, 262

Methyl (2*Z*)-2-azido-3-(2-chloropyridin-3-yl)acrylate: 2-Propenoic acid, 2-azido-3-(2-chloro-3-pyridinyl)-, methyl ester; (688357-18-8) **84**, 262

N-Methyl-*O*-benzoylhydroxylamine hydrochloride: Methanamine, *N*-(benzoyloxy)-, hydrochloride; **(**27130-46-7) **84**, 233

METHYL (*R*)-(–)-3-BENZYLOXY-2-METHYL PROPANOATE: Propanoic acid, 2-methyl-3-(phenylmethoxy)-, methyl ester, (2*R*)-; (112068-34-5) **84**, 295

Methyl bromoacetate: Acetic acid, bromo-, methyl ester; (96-32-2) **84**, 262

Methyl 2-bromomethyl-3-nitrobenzoate: Benzoic acid, 2-bromomethyl-3-nitro-, methyl ester; (98475-07-1), **80**, 75

Methyl *tert*-butyl ether; Propane, 2-methoxy-2-methyl-; (1634-04-4), **81**, 195; **82**, 69

2-Methyl-3-butyn-2-ol: 3-Butyn-2-ol, 2-methyl-; (115-19-5), **80**, 93

Methyl chloroformate: Carbonochloridic acid, methyl ester; (79-22-1) **84**, 88

METHYL 4-CHLORO-1*H*-PYRROLO[3,2-C]PYRIDINE-2-CARBOXYLATE: 1*H*-Pyrrolo[3,2-c]pyridine-2-carboxylic acid, 4-chloro-, methyl ester; (688357-19-9) **84**, 262

Methyl cyanoformate: Carbonocyanidic acid, methyl ester (9CI); (17640-15-2) **84**, 306

(*R*)-(+)-6-Methylcyclohex-2-en-1-one: (6*R*)-6-Methyl-2-cyclohexen-1-one; (62392-84-1) **82**, 108

(+)-(1*R*,2*S*,9*S*)-11-METHYL-7,11-DIAZATRICYCLO[7.3.1.0^{2,7}]TRIDECANE: 1,5-

Methano-2*H*-pyrido[1,2-*a*][1,5]diazocine, decahydro-3-methyl-, (1*R*,5*S*,11a*S*)-; (475301-86-1) **83**, 141

(*E*)-METHYL 2-DIAZO-4-PHENYLBUT-3-ENOATE: (119987-21-2) **84**, 334

N-Methyldicyclohexylamine: Cyclohexanamine, *N*-cyclohexyl-*N*-methyl-; (7560-83-0), **81**, 63, 64

(*S*)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (159497-37-7) **83**, 70

1-Methyl-3,4-dihydronaphthalene: Naphthalene, 1,2-dihydro-4-methyl-; (4373-13-1) **84**, 334

Methyl 2-ethenyl-3-nitrobenzoate: Benzoic acid, 2-ethenyl-3-nitro-, methyl ester; (195992-04-2), **80**, 75

(4*S*)-(1-METHYLETHYL)-5,5-DIPHENYLOXAZOLIDIN-2-ONE: 2-Oxazolidinone, 4-(1-methylethyl)-5,5-diphenyl-, (4*S*)-; (184346-45-0), **80**, 57

(η^5-(*S*)-2-(4-METHYLETHYL)OXAZOLINYLCYCLO-PENTADIENYL)-(η^4-TETRAPHENYLCYCLOBUTADIENE)COBALT: Cobalt, [1,1',1",1'"-(η4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]][(1,2,3,4,5-η)-1-[[[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,4-cyclopentadien-1-yl]-; (222400-02-4) **84**, 139, 148

(±)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester; (4538-50-5) **83**, 162

(*S*)-METHYL GLYCIDATE: Oxiranecarboxylic acid, methyl ester, (2*S*)-; (118712-39-3) **83**, 162

Methyl 5-hexenoate: 5-Hexenoic acid, methyl ester; (2396-80-7), **80**, 111

N-Methylhydroxylamine hydrochloride: Methanamine, *N*-hydroxy-, hydrochloride; (4229-44-1) **84**, 233

Methyl (*R*)-(–)-3-hydroxy-2-methyl propionate; Propanoic acid, 3-hydroxy-2-methyl-, methyl ester, (2*R*)-; (72657-23-9) **84**, 295

N-Methylimidazole: *1H*-lmidazole, 1-methyl-; (616-47-7), **81**, 236

METHYL INDOLE-4-CARBOXYLATE: *1H*-Indole-4-carboxylic acid, methyl ester; (39830-66-5), **80**, 75

Methyl iodide: Methane, iodo-; (74-88-4), **80**, 57, 144

Methyl 4-iodobenzoate: Benzoic acid, 4-iodo-, methyl ester; (619-44-3), **81**, 78

Methyllithium: Lithium, methyl-; (917-54-4), **81**, 16

Methyllithium-lithium bromide; (332360-06-2) **82**, 108

Methylmagnesium bromide: Magnesium, bromomethyl-; (75-16-1) **82**, 22

(*S,E*)-METHYL 2-((*R*)-4-METHYL-1,2-DIHYDRONAPHTHALEN-2-YL)-4-PHENYLBUT-3-ENOATE: 2-Naphthaleneacetic acid, 1,2-dihydro-4-methyl-α-[(1E)-2-phenylethenyl]-, methyl ester, (αS,2R)-; (76531-50-5) **84**, 334

Methyl 2-methyl-3-nitrobenzoate: Benzoic acid, 2-methyl-3-nitro-, methyl ester; (59382-59-1), **80**, 75

METHYL 5-METHYLPYRIDINE-2-CARBOXYLATE: 2-Pyridinecarboxylic acid, 5-methyl-, methyl ester; (260998-85-4), **80**, 133

(–)-Methyl (1*R*,9*R*)-6-Oxo-7,11-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4-diene-11-carboxylate: 1,5-Methano-2*H*-pyrido[1,2-*a*][1,5]diazocine-3(4*H*)-carboxylic acid, 1,5,6,8-tetrahydro-8-oxo-, methyl ester, (1*R*,5*R*)-; (125109-97-9) **83**, 141

Methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate: 1-Naphthalenecarboxylic acid, 1,2,3,4-tetrahydro-2-oxo-, methyl ester; (31202-23-0) **84**, 347

2-Methyl-2-[(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]propanamide: Propanamide, 2-methyl-2-[(5,6,7,8-tetrahydro-5-oxo-2- naphthalenyl)oxy]-; (418761-91-8) **84**, 325

(*E*)-2-METHYL-3-PHENYLACRYLIC ACID BUTYL ESTER: 2-PROPENOIC ACID, 2-METHYL-3-PHENYL-, BUTYL ESTER, (2*E*)-; (21511-00-5), **81**, 63

anti-5-METHYL-1-PHENYL-6-HEPTEN-3-OL (221366-16-1) **83**, 88
anti-3-METHYL-1-PHENYL-4-PENTEN-1-OL (205883-12-1) **83**, 88
N-[(4-Methylphenyl)sulfonyl(phenyl)methyl] *P,P*-diphenylphosphinic amide; (701291-86-3) **83**, 5
METHYL PHENYL SULFOXIDE: Benzene, (methylsulfinyl)-; (1193-82-4), **80**, 184
(R_S)-(+)-2-METHYL-2-PROPANESULFINAMIDE [*TERT*-BUTANESULFINAMIDE]: 2-Propanesulfinamide, 2-Methyl-, [*S*(*R*)]-; (196929-78-9) **82**, 157
N-Methylpyrrolidinone: 2-Pyrrolidinone, 1-methyl-; (872-50-4), **81**, 34; **82**, 69
4-METHYLPYRROLO[1,2-*a*]QUINOLINE; (796843-24-8) **83**, 103
trans-β-Methylstyrene: Benzene, (1*E*)-1-propenyl-; (873-66-5), **80**, 9
(*R,R*)-*trans*-β-METHYLSTYRENE OXIDE: Oxirane, 2-methyl-3-phenyl-, (2*R*,3*R*)-; (14212-54-5), **80**, 9
Methyl trifluoromethanesulfonate: Methyl trifluoromethanesulfonate; (333-27-7) **84**, 295
Methyltrioxorhenium: Rhenium, methyltrioxo-, (T-4); (70197-13-6), **81**, 204
Methyl(triphenylphosphine)gold (CH_3AuPPh_3); (23108-72-7) **83**, 55
Methyl tris(isopropoxy)titanium: Titanium, methyltris2-propanolato)-, (T-4)-; (18006-13-8), **81**, 16
Methyl vinyl ketone: 3-Buten-2-one; (78-94-4), **80**, 195
Mitsunobu reaction, **81**, 141
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Molybdenum(V) chloride; (10241-05-1) **84**, 163
Morpholine; (110-91-8) **84**, 22
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1-Morpholinopropan-1-one: 4-(1-oxopropyl)-morpholine; (30668-14-5) **84**, 22
(2*S*)-(–)-3-exo-(MORPHOLINO)ISOBORNEOL [(–)-MIB] **82**, 87

Natural product isolation **83**, 141
Negishi coupling, **81**, 77
(*S*)-(+)-Neomenthyldiphenylphosphine: Phosphine, [(1*S*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]diphenyl-; (43077-29-8) **84**, 111
Neopentyl glycol: 1,3-Propanediol, 2,2-dimethyl-; (126-30-7), **80**, 144; **81**, 134
Nickel(II) acetylacetonate: Bis(2,4-pentanedionate), nickel(II); (3264-82-2) **83**, 88
Ni(cod)$_2$: Nickel, bis[(1,2,5,6-**η**)-1,5-cyclooctadiene]-; (1295-35-8) **84**, 111
Nitration, **81**, 98
Nitrone synthesis, **81**, 204
p-Nitrophenol: 4-Nitrophenol; (100-02-7) **84**, 163, 177
1,8-Nonadiyne; (2396-65-8) **83**, 55
2,8-NONANEDIONE; (30502-73-9) **83**, 55
4-NONYLBENZOIC ACID: Benzoic acid, 4-nonyl-; (38289-46-2), **81**, 33
(Nonylmagnesium bromide: Magnesium, bromononyl-; (39691-62-8), **81**, 33
(Norbornadiene)rhodium chloride dimer; Rhodium, bis[(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene]di-μ-chlorodi-; (12257-42-0) **82**, 22

Octanoic acid; (124-07-2) **84**, 285
1-Octyne; (629-05-0) **84**, 77
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$Pd(dba)_2$: Palladium, bis[(1,2,4,5-η)-1,5-diphenyl-1,4-pentadien-3-one]- (9); (32005-36-0), **81**, 45, 55
Palladium (II) acetate: Acetic acid, palladium(2+) salt; (3375-31-3)), **80**, 75; **81**, 90; **84**, 148, 215, 317
Palladium chloride: Palladium chloride ($PdCl_2$); (7647-10-1), **81**, 56
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α-Phenethyl alcohol: Benzenemethanol, α-methyl-; (98-85-1) **84**, 102
Phenethylmagnesium chloride: Magnesium, chloro(2-phenylethyl)-; (90878-19-6) **84**, 317
4-Phenyl-3-buten-2-one; (122-57-6) **83**, 177
1-Phenyl-1-butyne: 1-Butynylbenzene; (622-76-4) **84**, 111, 163
4-Phenylbutyric acid: Benzenebutanoic acid; (1821-12-1), **81**, 262
N-Phenylcarbamic acid methyl ester: Carbamic acid, phenyl-methyl ester; (2603-10-3), **81**, 112
1-Phenylcyclohexene: Benzene, 1-cyclohexen-1-yl-; (771-98-2), **80**, 9
(*R,R*)-1-PHENYLCYCLOHEXENE OXIDE: 7-Oxabicyclo[4.1.0]heptane, 1-phenyl-, (1*R*,6*R*)-; (17540-04-4), **80**, 9
4-PHENYL-5(*E*)-DECEN-2-ONE; (42521-58-4) **84**, 192
S-Phenyl diazothioacetate: Ethanethioic acid, diazo-, *S*-phenyl ester; (72228-26-3), **80**, 160

Phenyldimethylsilane: Silane, dimethylphenyl-; (766-77-8) **82**, 188

(*E*)-4-(2-PHENYLETHENYL)BENZONITRILE: BENZONITRILE, 4-[(1*E*)-2-PHENYLETHENYL]- (9); (13041-79-7), **81**, 63

(*S*)-1-Phenylethylamine: Benzenemethanamine, α-methyl-, α*S*)-; (2627-86-3), **80**, 207

(*R*)-(+)-Phenylethylamine: Benzenemethanamine, **α**-methyl-, (**α**R)-; (3886-69-9) **84**, 306

(*S*)-[(1-Phenylethyl)amino]acetonitrile; Acetonitrile, [[(1*S*)-1-phenylethyl]amino]-; (35341-76-5), **80**, 207

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(4*S*)-4-(2-PHENYLETHYL)-2-OXETANONE: (4*S*)-4-(2-phenylethyl)-2-oxetanone; (214853-90-4) **82**, 170

(*R*)-(–)-2-Phenylglycinol: Benzeneethanol, β-amino-, (β*R*)-; (56613-80-0), **80**, 46

1-PHENYLHEX-5-EN-3-AMINE: Benzenepropanamine, α-2-propenyl-; (17125-07-4) **83**, 170

N-PHENYL-5*R*-HYDROXYMETHYL-2-OXAZOLIDINONE: 2-Oxazolidinone, 5-(hydroxymethyl)-3-phenyl-, (5*R*); (875080-42-7), **81**, 112

Phenylmagnesium bromide: Magnesium, bromophenyl-; (100-58-3), **80**, 57; **83**, 31

Phenylmagnesium chloride: Magnesium, chlorophenyl-; (100-59-4) **84**, 306

N-[(Phenyl)methylene]-*P,P*-diphenylphosphinic amide: Phosphinic amide, *P*,*P*-diphenyl-*N*-(phenylmethylene)-; (67764-52-7) **83**, 5

4-PHENYLMORPHOLINE: (92-53-5) **83**, 31

(*R*)-4-Phenyl-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-, (4*R*)-; (90319-52-1), **81**, 147; **84**, 359

5-PHENYLPENT-2-YN-1-OL: 2-Pentyn-1-ol, 5-phenyl-; (16900-77-9), **81**, 2

R-4-PHENYL-3-(1,2-PROPADIENY)-2-OXAZOLIDINONE: 2-OXAZOLIDINONE, 4-PHENYL-3-(1,2-PROPADIENYL)-, (4*R*)-; (256382-50-0), **81**, 147

(1*S*)-1-Phenylpropan-1-amine hydrochloride: Benzenemethanamine, α-ethyl-, hydrochloride, (α*S*)-: (19146-52-2) **83**, 5

3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0), **81**, 2; **83**, 170

N-[(*1S*)-1-Phenylpropyl]-*P,P*-diphenylphosphinic amide: Phosphinic amide, *P,P*-diphenyl-*N*-[(*1S*)-1-phenylpropyl]-; (106651-15-4) **83**, 5

3-Phenyl-2-propylthio-2-propen-1-ol, **80**, 190

3-Phenyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-phenyl-; (1504-58-1), **80**, 190

R-4-Phenyl-3-(2-propynyl)-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-3-(2-propynyl); (4*R*)-; (256382-74-8), **81**, 147

S-Phenyl thioacetate: Ethanethioic acid, *S*-phenyl ester; (934-87-2), **80**, 160

2-PHENYLTHIO-5-HEPTANOL: 3-Heptanol, 6-(phenylthio); (198778-75-5), **81**, 244

4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE: 2-Butanone, 4,4,4-trifluoro-3-(phenylmethyl)-; (808105-43-3) **83**, 177

(*R*)-4-PHENYL-3-(2-TRIISOPROPYLSILYL-ETHYNYL) OXAZOLIDIN-2-ONE: [2-Oxazolidinone, 4-phenyl-3-(2-triisopropylsilyl-ethynyl)-, (4*R*)-]; (503590-28-1) **84**, 359

Phosphorus oxychloride: Phophoric trichloride; (10025-87-3), **80**, 200

Phosphorus pentasulfide; (1314-80-3) **84**, 68

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Pinacol: 2,3-Butanediol, 2,3-dimethyl-; (76-09-5), **81**, 89

Pinacolborane: 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane; (25015-63-8) **82**, 126

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(+)-α-Pinene: (1*R*)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-ene; (7785-70-8) **83**, 24

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4-Piperidone monohydrate hydrochloride: 4-Piperidinone, hydrochloride; (41979-39-9), **81**, 214
Pivaloyl chloride: Propanoyl chloride, 2,2-dimethyl-; (3282-30-2), **81**, 226, 254
Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex: Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complex; (68478-92-2), **81**, 55
cis-Polybutadiene; (40022-03-5) **83**, 200
Potassium *tert*-butoxide: 2-Propanol, 2-methyl-, potassium salt; (865-47-4) **80**, 57, 144; **81**, 141; **82**, 87; **84**, 334
Potassium cyanide: Potassium cyanide [K(CN)]; (151-50-8), **81**, 214
Potassium *O*-ethyl xanthate: Carbonodithioic acid, *O*-ethyl ester, potassium salt; (140-89-6) **84**, 32
Potassium hexamethyldisilazide: Silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-, potassium salt; (40949-94-8) **84**, 88
Potassium hydrogen fluoride: (7789-29-9) **84**, 317
Potassium hydroxide; (1310-58-3) **82**, 1, 22, 179
Potassium nitrate:; (7757-79-1), **81**, 99
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Propanethiol; (79869-58-2), **80**, 190
Propanoic acid, 2-hydroxy-, ethyl ester, (2*S*)-; (687-47-8), **81**, 157
2-Propanol; (67-63-0) **82**, 10
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Propargyl benzoate: 2-Propyn-1-ol, benzoate; (6750-04-5) **83**, 200
Propargyl bromide: 1-Propyne, 3-bromo-; (106-96-7), **81**, 148
Propargylic alcohol synthesis, **81**, 2, 157
N-(2-Propenyl-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl-; (50487-71-3), **80**, 93
N-(2-Propenyl)-*N*-(2-propynyl)-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl-*N*-2-propynyl-; (133886-40-5), **80**, 93
Propiolic acid: 2-Propynoic acid; (471-25-0), **80**, 129
Propyl formate: Formic acid, propyl ester; (110-74-7) **82**, 18
1-(2-(1-Propynyl)phenyl)pyrrole: *1H*-Pyrrole, 1-[2-(1-propynyl)phenyl]-; (796843-21-5) **83**, 103
Pyridine; (110-86-1), **80**, 93, 177; **81**, 3; **82**, 147
Pyridinium chlorochromate: Chromate(1-), chlorotrioxo-, (T-4)-, hydrogen compound with pyridine (1:1); (26299-14-9), **80**, 1; **82**, 108
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3-PYRIDIN-3-YLQUINOLINE: Quinoline, 3-(3-pyridinyl)-; (96546-80-4), **81**, 89
3-PYRIDYLBORONIC ACID: Boronic acid, 3-pyridinyl-; (1692-25-7), **81**, 89
Pyrophosphate synthesis, **80**, 219

(*S*)-Quinap: Isoquinoline, 1-[2-(diphenylphosphino)-1-naphthalenyl]-, (1*S*)-; (149341-33-3) **84**, 1

Quinidine: Cinchonan-9-ol, 6'-methoxy-, (9*S*)-; (56-54-2) **82**, 120
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RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH$(C_6H_5)NH_2$](η^6-*p*-cymene): Ruthenium, [*N*-[(*1S,2S*)-2-(amino-κ*N*)-1,2-diphenylethyl]-4-methyl-benzenesulfonamidato-κ*N*]chloro-[(1,2,3,4,5,6-η)-1-methyl-4-(1-methylethyl)benzene]-; (192139-90-5) **82**, 10; **84**, 120

Salicyl alcohol: Benzenemethanol, 2-hydroxy-; (90-01-7), **81**, 171
Saponification **83**, 209; **84**, 325
Schwartz's reagent: Zirconium, chlorobis(η^5-2,4-cyclopentadien-1-yl)hydro- (9); (37342-97-5) **84**, 192
Silane, [(2,3-dihydro-1*H*-inden-2-yl)oxy](1,1-dimethylethyl)dimethyl-; (216884-03-6) **83**, 155

Silver carbonate: Carbonic acid, disilver(1+) salt; (534-16-7) **82**, 75
Silver trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, silver(1+) salt; (2923-28-6) **84**, 222
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Sodium amide: Sodium amide ($NaNH_2$); (7782-92-5), **80**, 144; **82**, 140
Sodium azide; (26628-22-8) **84**, 262, 347
Sodium benzophenone ketyl: Benzophenone, radical ion (1-), sodium (8); Methane, diphenyl-, radical ion (1-), sodium (9); (3463-17-0) **84**, 192
Sodium bicarbonate: Carbonic acid monosodium salt; (144-55-8) **82**, 75
Sodium bisulfite: Sulfurous acid, monosodium salt; (7631-90-5) **82**, 30, 75
Sodium *tert*-butoxide: 2-Propanol, 2-methyl-, sodium salt; (865-48-5) **84**, 163
Sodium carbonate: Carbonic acid disodium salt; (497-19-8) **82**, 55
Sodium chlorite: Chlorous acid, sodium salt; (7758-19-2), **81**, 195
Sodium cyclopentadienide: Sodium, 2,4-cyclopentadien-1-yl-; (4984-82-1) **84**, 139
Sodium dithionite: Dithionous acid, disodium salt; (7775-14-6), **80**, 227
Sodium fluoride: Sodium fluoride (NaF); (7681-49-4), **80**, 172
Sodium hexafluoroacetylacetonate: 2,4-Pentanedione, 1,1,1,5,5,5-hexafluoro-, ion(1-), sodium; (22466-49-5) **84**, 148
Sodium hydride: Sodium hydride (NaH); (7646-69-7), **81**, 147; **84**, 177, 347
Sodium hydrogen sulfite: Sulfurous acid, monosodium salt: (7631-90-5) **82**, 1
Sodium hypochlorite: Hypochlorous acid, sodium salt (8,9); (7681-52-9), **81**, 195; **82**, 80
Sodium iodide: Sodium iodide (NaI); (7681-82-5) **81**, 77, 121; **84** 347
Sodium metaperiodate: Periodic acid (HIO_4), sodium salt; (7790-28-5), **81**, 171
Sodium methoxide: Methanol, sodium salt; (124-41-4), **80**, 133
Sodium nitrite: Nitrous acid, sodium salt; (7632-00-0), **80**, 133
Sodium tetrafluoroborate; (13755-29-8) **82**, 166
Sodium thiosulfate: Thiosulfuric acid ($H_2S_2O_3$), disodium salt; (7772-98-7), **81**, 78; **82**, 157
Solid supports, **81**, 235
(–)-Sparteine: 7,14-Methano-2*H*,6*H*-dipyrido[1,2-*a*:1',2'-*e*][1,5]diazocine, dodecahydro-, (7*S*,7a*R*,14*S*,14a*S*)-; (90-39-1) **82**, 22
9-SPIROEPOXY-*endo*-TRICYCLO[5.2.2.0^{2,6}]UNDECA-4,10-DIEN-8-ONE: Spiro[4,7-ethano-*1H*-indene-8,2'-oxiran]-9-one, 3*a*,4,7,7*a*-tetrahydro-; (146924-02-9), **81**, 171
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TETRABENZYL PYROPHOSPHATE: Diphosphoric acid, tetrakis(phenylmethyl) ester; (990-91-0), **80**, 219
Tetrabutylammonium bromide: 1-Butanaminium, *N,N,N*-tributyl-, bromide; (1643-19-2), **80**, 227
Tetrabutylammonium fluoride: 1-Butanaminium, *N,N,N*-tributyl-, fluoride; (429-41-4) **83**, 111; **84**, 1

Tetrabutylammonium fluoride trihydrate: 1-Butanaminium, *N,N,N*-tributyl, fluoride, trihydrate; (87749-50-6), **81**, 45, 55
Tetrabutylammonium hydrogen sulfate: 1-Butanaminium, *N,N,N*-tributyl-, sulfate (1:1); (32503-27-8), **80**, 9
Tetrabromothiophene; (3958-03-0) **83**, 209
Tetrachloromethane: Methane, tetrachloro-; (56-23-5) **82**, 18
9-Tetradecylcarbazole: 9-Tetradecyl-9*H*-carbazole; (20863-25-6) **84**, 177
Tetrafluoroboric acid: Borate(1-), tetrafluoro-, hydrogen (8,9); (16872-11-0) **82**, 80
2,3,11,11a-TETRAHYDRO-1*H*-BENZO[d]PYRROLO[1,2-a]AZEPIN-5(6*H*)-ONE: 5*H*-Pyrrolo[2,1-b][3]benzazepin-5-one, 1,2,3,6,11,11a-hexahydro-; (137125-37-2) **84**, 347
2,3,3α,4-TETRAHYDRO-2-[(4-METHYLBENZENE)SULFONYL]CYCLOPENTA-[C]PYRROL-5(*1H*)-ONE: Cyclopenta[*b*]pyrrol-5(1*H*)-one, 2,3,3*a*,4-tetrahydro-1-[(4-methylphenyl)sulfonyl]-; (205885-50-3), **80**, 93
Tetrakis(hydroxymethyl)phosphonium sulfate ("Pyroset-TKOW"): Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1); (55566-30-8), **80**, 85
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1-Tetralone: 1(2*H*)-Naphthalenone, 3,4-dihydro-; (529-34-0), **80**, 104; **84**, 334
β-Tetralone: 2(1*H*)-Naphthalenone, 3,4-dihydro-; (530-93-8) **84**, 347
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1,1,3,3,-Tetramethyldisiloxane: Disiloxane, 1,1,3,3,-tetramethyl-; (3277-26-7), **81**, 54
N,N,N',N'-Tetramethylethylenediamine: 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl-; (110-18-9), **80**, 46
2,2,6,6-Tetramethylheptane-3,5-dione: 3,5-Heptanedione, 2,2,6,6-tetramethyl-: (1118-71-4) **82**, 69
2,2,6,6-Tetramethylpiperidine; Piperidine, 2,2,6,6-tetramethyl-; (768-66-1), **81**, 134
2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO): 1-Piperidinyoxy, 2,2,6,6-tetramethyl-; (2564-83-2), **81**, 195; **83**, 18
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Thioanisole: Benzene, (methylthio)-; (100-68-5), **80**, 184
Thiophenol: Benzenethiol; (108-98-5), **81**, 246
Thionyl chloride; (7719-09-7), **80**, 46; **84**, 32
Titanium tetrachloride: Titanium chloride ($TiCl_4$)(T-4); (7550-45-0), **81**, 16
$Ti(OEt)_4$: Ethanol, titanium(4+) salt; (3087-36-3) **84**, 129
Titanium tetraisoproproxide: 2-Propanol, titanium (4+)salt; (546-68-9) **80**, 120; **81**, 16
Toluene: Benzene, methyl-; (108-88-3) **82**, 55
N-p-Toluenesulfinamide: Benzenesulfinamide, 4-methyl-; (6873-55-8) **84**, 129
p-Toluenesulfinic acid: Benzenesulfinic acid, 4-methyl-; (536-57-2) **83**, 5
N-p-Tolylsulfinyl-(*E*)-1-phenylethylideneimine: Benzenesulfinamide, 4-methyl-*N*-(1-phenylethylidene)-, [*N*(*E*)]-; (177468-94-9) **84**, 129
p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl-; (98-59-9) **80**, 93, 133; **81**, 77, 159
(1*S*,2*S*)-(+)-*N-p*-Toluenesulfonyl-1,2-diphenylethylenediamine: Benzenesulfonamide, *N,N*'-(1,2-diphenyl-1,2-ethanediyl)bis[4-methyl-, [*S*-(*R**,*R**)]-; (170709-41-8) **84**, 120
N-p-TOLYLSULFONYL-(*E*)-1-PHENYLETHYLIDENEIMINE: Benzenesulfonamide,

4-methyl-*N*-(1-phenylethylidene)-, (*E*)-; (163586-87-6) **84**, 129
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3,4,6-Tri-*O*-benzyl-D-glucal: D-*arabino*-Hex-1-enitol, 1,5-anhydro-2-deoxy-3,4,6-tris-*O*-(phenylmethyl)-; (55628-54-1), **81**, 225
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2,2,2-Trifluoroethyl trifluoroacetate: Acetic acid, trifluoro-, 2,2,2-trifluoroethyl ester; (407-38-5), **80**, 160
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(*rac*)-4-Triisopropylsilyl-3-butyn-2-ol: 3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-: (726202-65-9) **84**, 120
(*S*)-4-TRIISOPROPYLSILYL-3-BUTYN-2-OL: (*S*)-3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-; (901126-37-2) **84**, 120
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(*R*)-4-Trimethylsilyl-3-butyn-2-yl acetate: 3-Butyn-2-ol, 4-(trimethylsilyl)-, acetate; (129571-78-4) **82**, 43

(*R*)-4-Trimethylsilyl-3-butyn-2-yl mesylate: 3-Butyn-2-ol, 4-(trimethylsilyl)-, methanesulfonate, (2*R*)-; (200440-90-0) **82**, 43

(*S*)-4-Trimethylsilyl-3-butyn-2-yl succinate: Butanedioic acid, mono [(1*S*)-1-methyl-3-(trimethylsilyl)-2-propynyl] ester; (375395-73-6) **82**, 43

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(*Z*)-1-(Trimethylsilyl)-1-hexene: Silane, 1-hexenyltrimethyl-, (*Z*)-; (52835-06-0), **80**, 120

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Tris[*N*-(*tert*-butyl)(3,5-dimethylphenyl)-amido]molybdenum(III): (236740-70-8) **84**, 163

Tris(dibenzylideneacetone)dipalladium(0)–chloroform (1/1): Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-, compound with trichloromethane (1:1); (52522-40-4) **83**, 111
Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$]: Palladium, tris[**μ**-[(1,2-**η**:4,5-**η**)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-; (52409-22-0) **84**, 163, 177
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